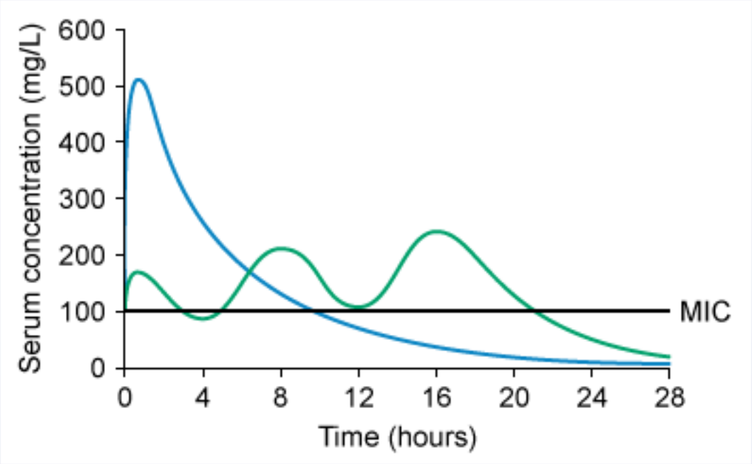
A novel aminoglycoside antibiotic is developed that is intravenously administered and excreted unchanged in urine with an elimination half-life of 4 hours. Two different dosing regimens are tested in a clinical trial: smaller doses given 3 times a day and a higher dose given once a day. The total administered drug amount per kilogram of body weight per day (mg/kg/day) is the same in both regimens. Serum drug concentration is monitored in both groups and is shown in the graph below:

[Blue: once-daily (extended interval) dosing, Green: multiple-daily dosing, MIC: minimum inhibitory concentration]



It is found that both regimens are effective against gram-negative pathogens, with clinical improvement occurring slightly earlier on average with once-daily dosing. Which of the following best explains the efficacy of once-daily dosing despite the short half-life of this antibiotic?

- A. Concentration-dependent killing
- B. High therapeutic index
- C. Linear dose–response relationship
- D. Low threshold dose

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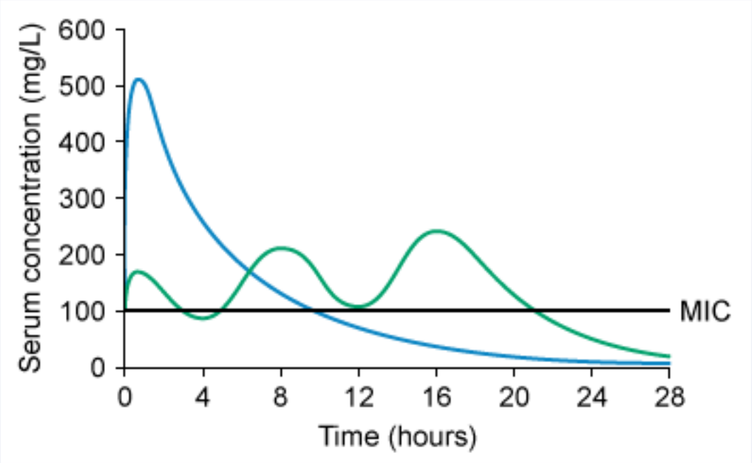
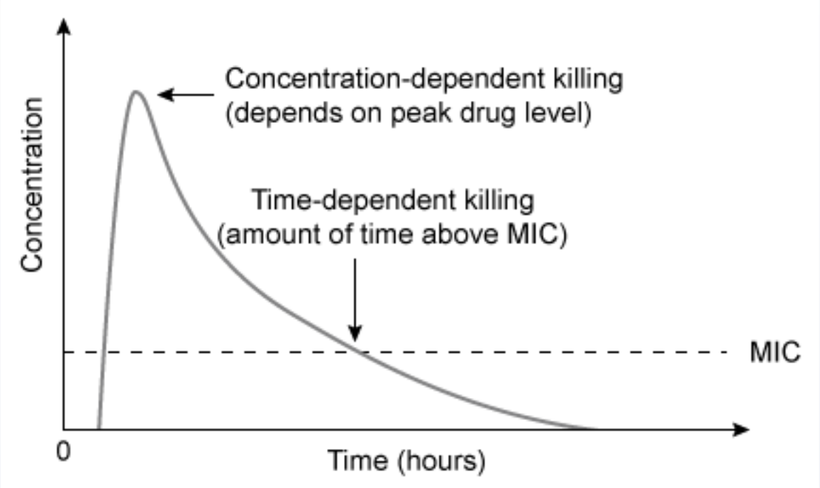


It is found that both regimens are effective against gram-negative pathogens, with clinical improvement occurring slightly earlier on average with once-daily dosing. Which of the following best explains the efficacy of once-daily dosing despite the short half-life of this antibiotic?

- A. Concentration-dependent killing (78%)
- B. High therapeutic index (7%)
- C. Linear dose–response relationship (5%)
- D. Low threshold dose (2%)
- E. Time-dependent killing (6%)

Explanation



The 2 major factors influencing the effectiveness of antimicrobial agents are the drug concentration at the target site and the amount of time that microbes are exposed to the drug. The relative contribution of these factors to drug efficacy depends on the particular agent. In general, antibiotics can be classified into 2 categories based on which factor is more important:

- **Concentration-dependent killing:** Antibiotics with this pattern of activity (eg, aminoglycosides, fluoroquinolones) have a persistent, suppressive effect on bacterial growth following a limited exposure, resulting in increased killing ability when drug levels at the site of infection are maximized. The **higher the peak drug level** compared to the minimum inhibitory concentration (MIC), the **greater the antimicrobial activity**. As such, higher-dose, **extended-interval** (ie, once-daily) regimens are frequently used to optimize bacterial killing.
- **Time-dependent killing:** Antibiotics with this activity pattern (eg, beta-lactams [penicillins, cephalosporins], clindamycin) have minimal persistent effects and are dependent on **long exposure durations** for their antimicrobial activity. They are more effective when serum concentrations **exceed the MIC** for a prolonged period. Therefore, more frequent, **multiple-daily dosing** regimens are used to maintain plasma concentrations greater than the MIC for as long as possible.

In this example, both treatment regimens were effective, with extended-interval dosing having a slightly better response time. This effect is best explained by the novel aminoglycoside exhibiting concentration-dependent killing **(Choice E)**.

0 Time (hours)

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In this example, both treatment regimens were effective, with extended-interval dosing having a slightly better response time. This effect is best explained by the novel aminoglycoside exhibiting concentration-dependent killing **(Choice E)**.

(Choice B) The therapeutic index (ie, [toxic dose]/[effective dose]) is a measurement of the relative safety of a drug; it is an intrinsic property upon which drug dosing regimens are devised. A relatively high therapeutic index is usually necessary to prevent toxicity with extended-interval dosing because the administered drug amounts lead to higher serum levels than seen with more frequent dosing regimens.

(Choice C) Most drugs exhibit a *sigmoid*-shaped dose response curve that shows no effect until a threshold concentration is exceeded. After this occurs, the effects increase with increasing drug concentration until a saturation threshold (ie, maximum effect) is reached. In contrast to this sigmoidal response, the risk of cancer following exposure to ionizing radiation shows a *linear* dose–response relationship (ie, risk increases proportionately with increased exposure).

(Choice D) The threshold dose is the lowest dose at which drug effects are first seen. In this case, both dosing regimens cause serum concentrations to rise above the MIC. Furthermore, the extended-interval dosing regimen results in less total time above the MIC but still demonstrates effectiveness. Therefore, a low dosing threshold does not explain the effectiveness of extended-interval dosing.

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Educational objective:
Antibiotics exibiting concentration-dependent killing can be administered using relatively high doses given at lower frequency. This allows for effective microbial killing while preventing adverse effects that may occur with prolonged systemic exposure.

Pharmacology	Infectious Diseases	Pharmacodynamics
Subject	System	Topic

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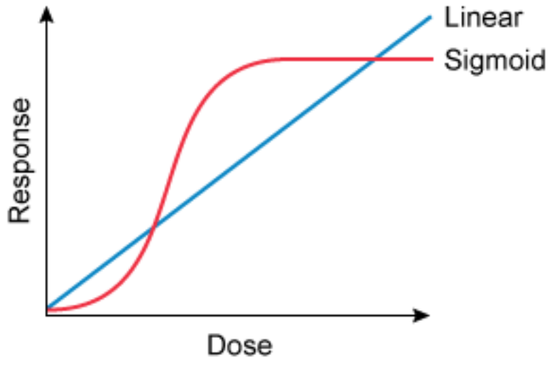

Zoom In Zoom Out Reset Add To Flash Card

A 65-year-old man comes to the emergency department due to fevers, chills, and confusion. He has a history of poorly controlled diabetes mellitus with a nonhealing ulcer of the left foot. His temperature is 38.3 C (101 F), blood pressure is 90/60 mm Hg, pulse is 112/min, and respirations are 22/min. On examination, there is slight erythema surrounding his left foot ulcer with foul-smelling discharge. No heart murmur is auscultated, the lungs are clear, and the abdomen is soft and nontender. Blood cultures are obtained, and he is started on broad-spectrum antibiotics. Twenty-four hours later, blood cultures grow β-lactamase-producing *Bacteroides* species. Which of the following is most likely to provide appropriate antimicrobial coverage for this patient?

A. Azithromycin
B. Ceftriaxone
C. Ciprofloxacin
D. Piperacillin-tazobactam
E. Vancomycin

Submit

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- A. Azithromycin (9%)
- B. Ceftriaxone (10%)
- C. Ciprofloxacin (14%)
- ✓ D. Piperacillin-tazobactam (51%)
- E. Vancomycin (14%)

Omitted
Correct answer
D

51%
Answered correctly

02 secs
Time Spent

05/10/2020
Last Updated

Explanation

Areas of necrosis and diminished blood supply (such as chronic, nonhealing ulcers) facilitate the growth of anaerobes. ***Bacteroides*** are gram-negative **anaerobic** rods that can produce β-lactamase, an enzyme that breaks down penicillins. **β-lactamase inhibitors** such as tazobactam, clavulanic acid, and sulbactam prevent these enzymes from functioning. The **combination** of piperacillin (extended-spectrum penicillin) and tazobactam is effective against a large number of gram-positive, gram-negative, and anaerobic bacteria and would be the most appropriate option

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(Choice A) Azithromycin is a macrolide antibiotic that binds to the 50S subunit of bacteria ribosomes, thereby inhibiting protein synthesis. It is used for infections with *Chlamydia, Mycoplasma, Haemophilus influenzae,* and *Moraxella catarrhalis*. Anaerobic activity against many *Fusobacterium* and some *Bacteroides* species may be limited.

(Choice B) Ceftriaxone is a third-generation parenteral cephalosporin with poor anaerobic activity. It is active against *H influenzae, Klebsiella pneumoniae*, and *Neisseria* and *Serratia* species.

(Choice C) Ciprofloxacin is a second-generation quinolone that acts by interfering with bacterial DNA gyrase (topoisomerase II). Ciprofloxacin is active against most gram-negative rods and bacilli, including *Legionella* and *Pseudomonas aeruginosa*. It is not effective against anaerobic infections.

(Choice E) Vancomycin is a tricyclic glycopeptide that inhibits the synthesis of peptidoglycan, a main component of the cell wall of gram-positive bacteria. It is used against methicillin-resistant *Staphylococcus aureus* as well as *Clostridium difficile*.

Educational objective:
Piperacillin-tazobactam is a combination of extended-spectrum penicillin with β-lactamase inhibitor. It is effective against most gram-negative enteric rods (including *Pseudomonas aeruginosa*) and against *Bacteroides fragilis*.

Pharmacology	Infectious Diseases	Diabetic foot
Subject	System	Topic

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A phase II trial is being conducted at an academic medical center to assess the safety and efficacy of a novel antifungal medication that has yielded promising results in preclinical studies. The medication is known to inhibit fungal colony growth by changing the composition of the fungal cell membrane. Phase 0 and phase I trials on healthy volunteers have been uneventful. The current phase II trial includes 175 subjects. In 168 subjects, the new antifungal agent is found to inhibit liver cytochrome P450-dependent metabolism of several drugs. Based on these data, the new antifungal agent is most similar to which of the following?

A. Amphotericin B
B. Caspofungin
C. Flucytosine
D. Griseofulvin
E. Itraconazole

Submit

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A. Amphotericin B (13%)
B. Caspofungin (5%)
C. Flucytosine (2%)
D. Griseofulvin (16%)
✓ E. Itraconazole (61%)

Omitted
Correct answer
E

61%
Answered correctly

02 secs
Time Spent

05/04/2020
Last Updated

Explanation

Azoles are antifungal medications that inhibit the demethylation of lanosterol into ergosterol in fungal cells. They exert their antifungal effects by suppressing synthesis of **ergosterol**, an essential component of the fungal cell **membrane**. However, azoles also **inhibit** the activity of the human **P450** cytochrome oxidase system. This property leads to multiple drug-drug **interactions**.

All azoles (eg, ketoconazole, fluconazole, itraconazole, voriconazole) increase the serum concentrations of drugs metabolized by liver P450 enzymes. This means that, when used concomitantly with azoles, drugs metabolized by the liver P450 system may have **increased** toxicity. For

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Cytochrome oxidase inducers (eg, rifampin, phenytoin, carbamazepine, phenobarbital) increase azole metabolism, thereby lowering azole concentration in serum.

(Choice A) Amphotericin B is a polyene antifungal that binds ergosterol in the fungal cell membrane, leading to pore formation and cell lysis.

(Choice B) 1,3-beta-D-glucan is a major polysaccharide component of the fungal cell wall. Caspofungin and the other echinocandin antifungals block glucan synthesis.

(Choice C) Flucytosine inhibits the synthesis of both DNA (replication) and RNA (protein synthesis) in fungal cells. It is mainly used as a synergistic agent with amphotericin B. This drug combination is particularly important in the treatment of cryptococcal meningitis.

(Choice D) Griseofulvin, a P450 inducer, enters fungal cells and binds microtubules, inhibiting mitosis.

Educational objective:
Azoles inhibit the synthesis of ergosterol by the fungal cytochrome P450 enzymes. They also suppress the human P450 system, resulting in many drug-drug interactions.

Pharmacology	Infectious Diseases	Azoles
Subject	System	Topic

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A 76-year-old hospitalized woman is evaluated for persistent fevers. Four days ago, she was admitted to the hospital for sepsis, for which she has received broad-spectrum empiric intravenous antibiotic therapy. Her temperature is 38.9 C (102 F), blood pressure is 110/80 mm Hg, pulse is 98/min, and respirations are 18/min. Cardiac examination reveals a new diastolic murmur. Multiple blood cultures drawn at different times grow *Enterococcus*. Echocardiogram reveals mitral valve vegetation suggestive of endocarditis. An intravenous antibiotic is added to the patient's treatment regimen for synergy. Several days later, she develops tinnitus and hearing loss attributed to this antibiotic. The additional antibiotic most directly affects which of the following processes?

- A. Cell wall cross-linking
- B. DNA unwinding
- C. Folic acid synthesis
- D. Maintenance of transmembrane potential
- E. mRNA genetic code reading
- F. tRNA charging

Submit

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- A. Cell wall cross-linking (18%)
- B. DNA unwinding (5%)
- C. Folic acid synthesis (4%)
- D. Maintenance of transmembrane potential (5%)
- ✓ E. mRNA genetic code reading (54%)
- F. tRNA charging (10%)

Omitted
Correct answer
E

54%
Answered correctly

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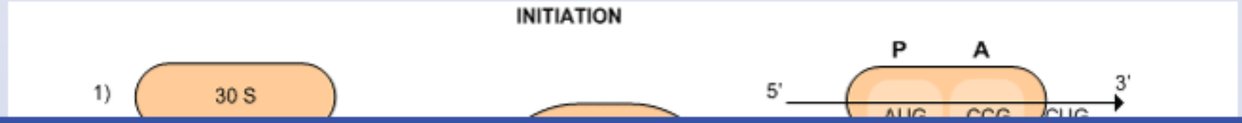
Time Spent

06/30/2020
Last Updated

Explanation



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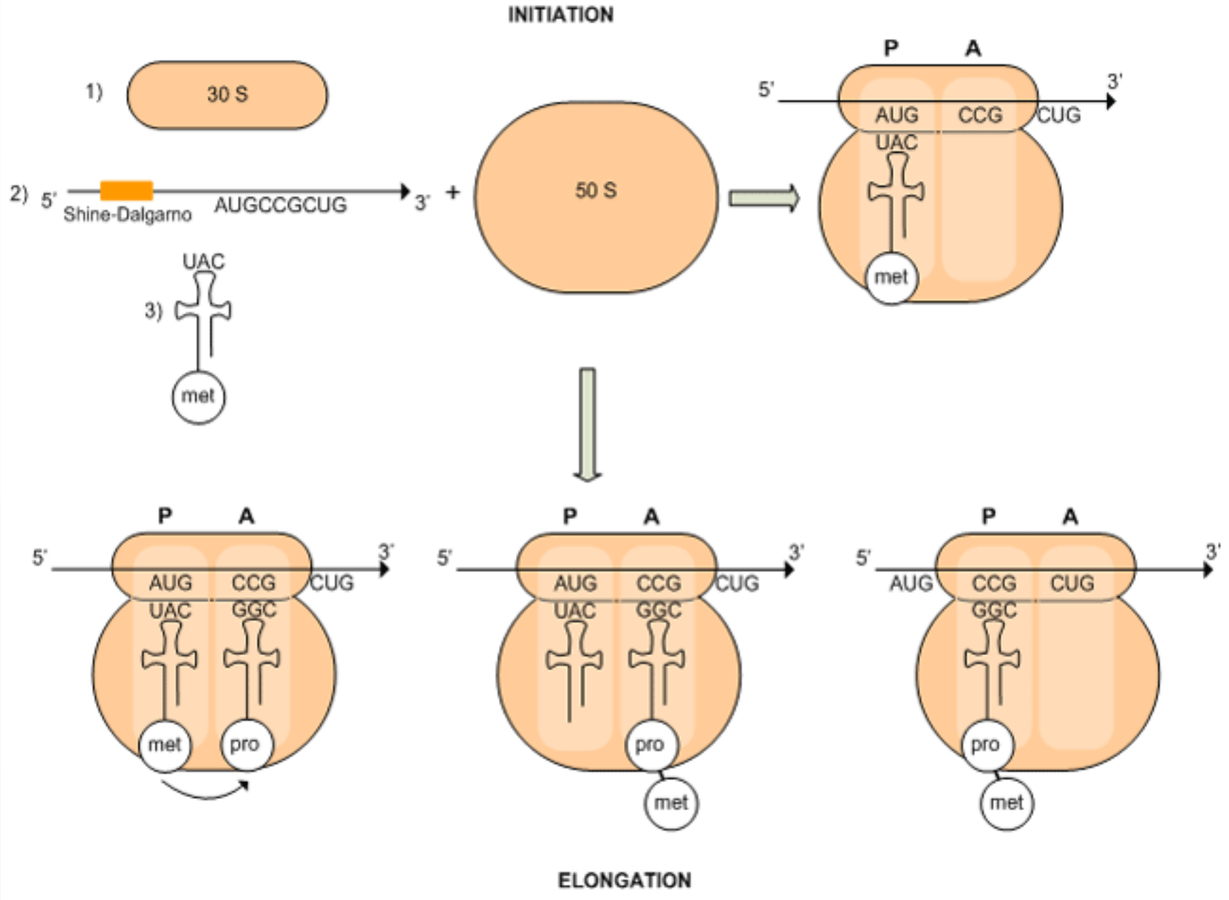

This patient with enterococcal endocarditis likely received an **aminoglycoside** (AG) such as gentamicin, a ribosome-targeting antibiotic. AGs are associated with **ototoxicity** (hearing loss, tinnitus) and **nephrotoxicity**.

mRNA is translated into amino acids (AAs) and proteins on ribosomes.

- The small ribosomal subunit (30S in prokaryotes, 40S in eukaryotes) binds mRNA, which contains genetic information serving as a reading frame, and tRNA, which serves as an AA carrier

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- The small ribosomal subunit (30S in prokaryotes, 40S in eukaryotes) binds mRNA, which contains genetic information serving as a reading frame, and tRNA, which serves as an AA carrier
- The larger ribosomal subunit (50S in prokaryotes, 60S in eukaryotes) contains peptidyltransferase, which catalyzes peptide bond formation between AAs

In **prokaryotes**, a unique mRNA sequence (Shine-Dalgarno) is located upstream from initiation codon AUG, which recognizes an N-formylmethionine-tRNA. This sequence allows 30S binding to mRNA and this N-formylmethionine-tRNA (forming the prokaryotic 30S **initiation complex**). The energy for this reaction (GTP hydrolysis) brings the 50S subunit into the initiation complex, resulting in a 70S ribosomal unit.

AGs irreversibly bind to **bacterial 30S** but not eukaryotic 40S; this causes **genetic code misreading** and bacterial protein synthesis inhibition. AGs also appear to impact **translocation**, whereby an aminoacyl-tRNA is shifted from the ribosomal A site (after initial binding) to the P site (after AA incorporation into the peptide chain during elongation) to the E site (after AA cleaving from its tRNA). The initial N-formylmethionine-tRNA notably binds at the P site.

(Choice A) AGs need to diffuse inside the cell to reach the ribosome. As a result, they are often prescribed **synergistically** in combination with antibiotics affecting cell wall synthesis. These include penicillins, which impact cell wall cross-linking, or vancomycin. Vancomycin is also associated with ototoxicity, but it is a glycopeptide antibiotic that acts by **directly** inhibiting peptidoglycan synthesis, **not** cell wall cross-linking (which occurs at a later stage of cell wall synthesis). Although *Enterococcus* is generally resistant to AGs, these drugs are routinely used as synergistic agents **in combination** with penicillins or vancomycin in patients with enterococcal endocarditis; such combinations lead to improved bacterial killing and are the standard of care for this condition.

(Choices B and C) Fluoroquinolones act on DNA gyrase to prevent DNA unwinding. Trimethoprim-sulfamethoxazole affects folic acid synthesis. These antibiotics are not classically associated with ototoxicity and are not used synergistically for enterococcal endocarditis.

(Choice D) Daptomycin disrupts the bacterial membrane by creating transmembrane channels that cause intracellular ion leakage and cellular membrane depolarization. Its main side effects are myopathy and rhabdomyolysis.

(Choice F) tRNA charging refers to initial covalent bonding between tRNA and the corresponding AA, facilitated by aminoacyl-tRNA synthetase;

formylmethionine-tRNA. This sequence allows 30S binding to mRNA and this N-formylmethionine-tRNA (forming the prokaryotic 30S **initiation complex**). The energy for this reaction (GTP hydrolysis) brings the 50S subunit into the initiation complex, resulting in a 70S ribosomal unit.

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Educational objective:
Aminoglycosides inhibit genetic code reading and protein synthesis by binding to the prokaryotic 30S ribosomal subunit.

Pharmacology	Infectious Diseases	Aminoglycoside
Subject	System	Topic

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A 33-year-old homeless man is hospitalized due to recent weight loss, odynophagia, and progressive cough. He is found to be HIV-positive and his CD4 count is 45/mm^3. The patient's condition improves on a newly instituted treatment, but 4 weeks later at outpatient follow-up he is found to have significantly elevated fasting blood glucose. Which of the following medications is most likely responsible for his hyperglycemia?

- A. Acyclovir
- B. Lopinavir
- C. Azithromycin
- D. Foscarnet
- E. Trimethoprim-sulfamethoxazole
- F. Zidovudine

Submit

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- A. Acyclovir (3%)
- ✓ B. Lopinavir (45%)
- C. Azithromycin (5%)
- D. Foscarnet (13%)
- E. Trimethoprim-sulfamethoxazole (8%)
- F. Zidovudine (23%)

Omitted
Correct answer
B

45%
Answered correctly

01 sec
Time Spent

02/29/2020
Last Updated

Explanation

Mechanism of action of HIV antiretroviral medications		
Class	**Example(s)**	**Mechanism of action**
NRTI	Tenofovir, emtricitabine, lamivudine, abacavir, zidovudine	Inhibits HIV DNA synthesis from RNA template by terminating DNA chain elongation

Mechanism of action of HIV antiretroviral medications		
Class	**Example(s)**	**Mechanism of action**
NRTI	Tenofovir, emtricitabine, lamivudine, abacavir, zidovudine	Inhibits HIV DNA synthesis from RNA template by terminating DNA chain elongation • NRTI: **Competitive** nucleoside/nucleotide RT inhibitor • NNRTI: **Allosteric** RT inhibitor
NNRTI	Efa**vir**enz, ne**vir**apine	
PI	Ataza**navir**, daru**navir**, indi**navir**, rito**navir**	Inhibits HIV polyprotein **cleavage**
Inte**gra**se inhibitor	Dolute**gravir**, ralte**gravir**	Inhibits HIV DNA integration into host genome
Fusion inhibitor	En**fu**virtide	Inhibits HIV fusion with target cell membrane by binding to HIV **gp41**
CCR5 antagonist	Maraviroc	Inhibits HIV entry by blocking the HIV **gp120allosteric** interaction with CCR5 (tropism testing required)

CCR5 = chemokine (C-C motif) receptor 5; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside/nucleotide reverse transcriptase inhibitor; **PI** = protease inhibitor; **RT** = reverse transcriptase.

Lopinavir is a **protease inhibitor (PI)**. These drugs reversibly inhibit viral protease, an enzyme responsible for HIV polyprotein cleavage to form mature viral proteins. PIs are never used as monotherapy as viral resistance to the entire class can form quickly. The following important adverse effects can be seen with PIs:

1. **Lipodystrophy** leads to increased fat deposition on the back and abdomen and decreased adipose tissue on the face, extremities, and buttocks. This gives patients a "buffalo hump" appearance with central obesity and peripheral wasting.
2. **Hyperglycemia** results from increased insulin resistance and may lead to diabetes.
3. **Inhibition of cytochrome P450** may cause interactions with other drugs. Rifampin increases P450 activity and will therefore decrease PI serum levels; as a result, rifampin can be replaced with rifabutin in the treatment of tuberculosis in patients on PIs.

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3. **Inhibition of cytochrome P450** may cause interactions with other drugs. Rifampin increases P450 activity and will therefore decrease PI serum levels; as a result, rifampin can be replaced with rifabutin in the treatment of tuberculosis in patients on PIs.

(Choice A) Acyclovir is an antiviral drug active against herpes simplex virus types 1 and 2 and varicella-zoster viruses. Renal toxicity is the most important side effect.

(Choice C) Azithromycin is a macrolide antibiotic used for treatment and prophylaxis of *Mycobacterium avium* complex infections in patients with HIV.

(Choice D) Foscarnet is used for the treatment of cytomegalovirus infections. It may cause nephrotoxicity and electrolyte disturbances (eg, hypocalcemia, hypomagnesemia, hypokalemia).

(Choice E) Trimethoprim-sulfamethoxazole (TMP-SMX) is used in patients with HIV for the prevention and treatment of pneumonia caused by *Pneumocystis jirovecii* (formerly *P carinii*). The most important side effects associated with TMP-SMX are megaloblastic anemia, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

(Choice F) Zidovudine is a nucleoside reverse transcriptase inhibitor (NRTI). NRTIs act by suppressing DNA synthesis from viral RNA. One of the most common side effects of zidovudine is bone marrow toxicity, resulting in anemia in up to 40% of patients.

Educational objective:
Protease inhibitors are HIV antiretroviral medications that inhibit cleavage of the polypeptide precursor into mature viral proteins. Their side effects as a class include hyperglycemia, lipodystrophy, and drug-drug interactions due to inhibition of cytochrome P450.

Pharmacology Infectious Diseases Antiretroviral therapy

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Pharmacology	Infectious Diseases	Antiretroviral therapy
Subject	System	Topic

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An 84-year-old woman is sent to the hospital from a nursing home due to 3 days of fever, abdominal pain, and progressive lethargy. The patient has a history of recurrent hospitalizations with multiple antibiotic courses for urinary tract infection, infected decubitus ulcer, and pneumonia. Her temperature is 38.2 C (101 F), blood pressure is 100/60 mm Hg, and pulse is 110/min. She has mild suprapubic and right costovertebral angle tenderness. Urine and blood cultures are obtained, and the patient is started on intravenous fluids and empiric ceftriaxone. Her urine culture shows extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*. Which of the following features is most likely to be found in this organism?

- A. DNA gyrase with altered A subunit
- B. Outer membrane with novel porin structure
- C. Penicillin-binding protein with reduced antibiotic affinity
- D. Peptidoglycan cell wall with amino acid modification
- E. Plasmid with drug resistance gene
- F. Ribosome with methylated 16S rRNA

Submit

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- A. DNA gyrase with altered A subunit (1%)
- B. Outer membrane with novel porin structure (4%)
- C. Penicillin-binding protein with reduced antibiotic affinity (30%)
- D. Peptidoglycan cell wall with amino acid modification (9%)
- ✓ E. Plasmid with drug resistance gene (52%)
- F. Ribosome with methylated 16S rRNA (1%)

Omitted
Correct answer
E

52%
Answered correctly

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Time Spent

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Explanation

Common antibiotic resistance mechanisms	
	• Beta-lactamase, ESBL

Common antibiotic resistance mechanisms	
Penicillins	• Beta-lactamase, ESBL • Mutated PBP • Mutated porin protein
Vancomycin	• Mutated peptidoglycan cell wall • Impaired influx/increased efflux
Quinolones	• Mutated DNA gyrase • Impaired influx/increased efflux
Aminoglycosides	• Aminoglycoside-modifying enzymes • Mutated ribosomal subunit protein • Mutated porin protein
Tetracyclines	• Impaired influx/increased efflux • Inactivated enzyme
Rifamycins	• Mutated RNA polymerase

ESBL = extended-spectrum beta-lactamase; PBP = penicillin-binding protein.

This patient has a urinary tract infection caused by an **extended-spectrum beta-lactamase** (ESBL)-producing *Escherichia coli*. ESBL enzymes can inactivate extended-spectrum penicillins and cephalosporins (including third- and fourth-generation cephalosporins) and monobactams (aztreonam). Genes encoding these enzymes are often located on **plasmids** and therefore can be transferred between organisms and between different species through conjugation. Some have been incorporated into bacterial chromosomes. **Carbapenems** (eg, imipenem) are the treatment of choice for ESBL-producing organisms (although unfortunately, organisms with carbapenem resistance have emerged).

(Choice A) Mutations in DNA gyrase can lead to fluoroquinolone resistance and generally do not impact beta-lactam antibiotic activity.

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(Choice B) Porin mutations can confer penicillin and aminoglycoside resistance and are particularly important in gram-negative organisms such as *Pseudomonas*.

(Choice C) Penicillin-binding protein alterations are the mechanism that leads to methicillin resistance in *Staphylococcus aureus*.

(Choice D) Vancomycin inhibits glycopeptide polymerization through binding to D-alanyl-D-alanine in the cell wall precursor; peptidoglycan changes (eg, D-alanine-D-lactate) can develop as a resistance mechanism.

(Choice F) Ribosome mutations can confer resistance to ribosome-targeting antibiotics such as aminoglycosides and macrolides.

Educational objective:
Extended-spectrum beta-lactamases can be produced by gram-negative bacteria, rendering cephalosporins and other beta-lactam antibiotics inactive. These genes can be transmitted between organisms through plasmid conjugation.

References

- Extended-spectrum beta-lactamase-producing organisms.
- Resistance in gram-negative bacteria: enterobacteriaceae.

Pharmacology	Infectious Diseases	Antibiotic resistance
Subject	System	Topic

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A 45-year-old woman is hospitalized due to severe *Pneumocystis* pneumonia. The patient has a history of injection drug use and was diagnosed with HIV 10 years ago. She does not adhere to antiretroviral therapy and has developed resistance to multiple antiretroviral medications. Laboratory evaluation reveals severe immunosuppression with a high HIV viral load. After the patient is adequately treated for pneumonia, HIV genotypic analysis is performed. The viral isolates are found to have a mutation in the variable (V3) region of the *env* gene, which makes the virus capable of infecting T cells with a specific surface receptor, but infection of macrophages is inefficient. Which of the following antiretroviral medications is most likely to be ineffective in this patient?

- A. Atazanavir
- B. Efavirenz
- C. Enfuvirtide
- D. Maraviroc
- E. Raltegravir
- F. Tenofovir

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- A. Atazanavir (2%)
- B. Efavirenz (5%)
- C. Enfuvirtide (22%)
- ✓ D. Maraviroc (59%)
- E. Raltegravir (4%)
- F. Tenofovir (5%)

Omitted
Correct answer
D

59%
Answered correctly

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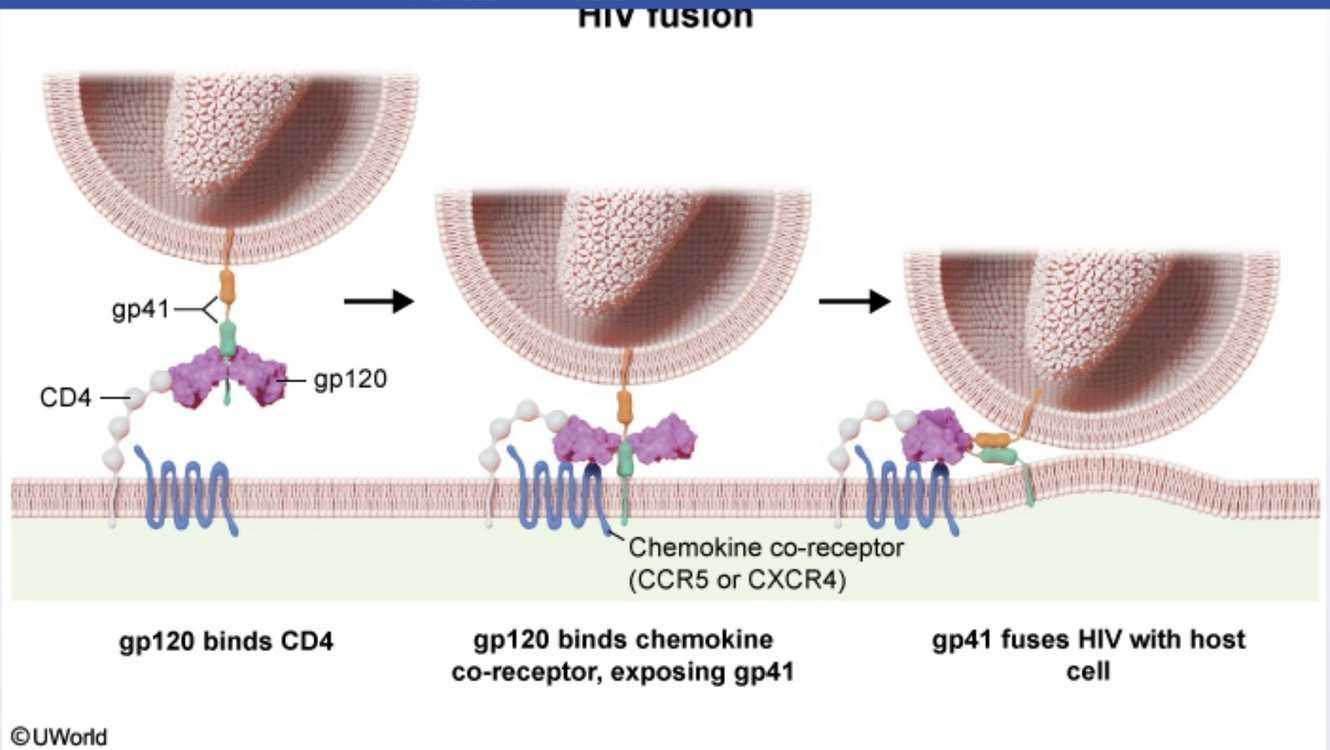
Explanation

HIV fusion



HIV binds to host cells using the host CD4 receptor and a chemokine coreceptor (either CCR5 or CXCR4). The virus preferentially targets T lymphocytes, dendritic cells, and macrophages because these cells contain high surface concentrations of CD4. However, each of these cell types contains different surface concentrations of the 2 chemokine receptors. HIV is considered **tropic** for a certain cell type, depending on whether it preferentially binds to CCR5 or CXCR4 for viral entry, as follows:

- **R5 virus** uses CCR5 for viral entry and is considered **macrophage-tropic** because CCR5 is expressed in high concentrations on both macrophages and lymphocytes. R5 is the predominant HIV type.
- **X4 virus** uses CXCR4 for viral entry and is considered **T lymphotropic** because CXCR4 is expressed primarily on T lymphocytes but only **minimally on macrophages**.

HIV trophism is determined by a gene sequence in the variable (V3) region of the ***env* gene**, which encodes for the HIV surface glycoprotein 120.

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

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HIV trophism is determined by a gene sequence in the variable (V3) region of the ***env* gene**, which encodes for the HIV surface glycoprotein 120. This glycoprotein mediates viral attachment to the CD4 receptor and chemokine coreceptor.

The laboratory results in this case indicate an X4 virus (T lymphotropic with minimal macrophage invasion). Patients with X4 virus cannot be treated with HIV medications that target CCR5 (eg, **maraviroc**) because the X4 virus uses CXCR4, not CCR5, to enter cells.

(Choice A) Protease inhibitors (eg, atazanavir, indinavir, darunavir) inhibit HIV protease from cleaving HIV polyproteins into the individual, functional proteins that compose the virus. This results in the formation of immature, noninfectious virions that are unable to infect T cells or macrophages.

(Choices B and F) Non-nucleoside reverse transcriptase inhibitors (eg, efavirenz, nevirapine) allosterically bind reverse transcriptase, which alters its shape and prevents it from converting the HIV RNA genome into complementary DNA (cDNA). Nucleoside reverse transcriptase inhibitors (eg, tenofovir, emtricitabine) competitively bind reverse transcriptase and are integrated into growing cDNA strands, which results in chain termination. Both of these HIV medication classes truncate viral replication but do not affect viral attachment or fusion.

(Choice C) Enfuvirtide is an HIV fusion inhibitor that binds to the HIV transmembrane surface protein glycoprotein 41 and prevents the virus from fusing with the host cell membrane. Fusion inhibitors would inhibit the ability of HIV to invade both lymphocytes and macrophages.

(Choice E) Integrase inhibitors (eg, raltegravir, dolutegravir) prevent the HIV enzyme integrase from incorporating viral cDNA into the host chromosome, which prevents viral replication. They do not affect viral attachment or fusion.

Educational objective:

HIV trophism is determined by a gene sequence in the variable (V3) region of the ***env* gene**, which encodes for the HIV surface glycoprotein 120. This glycoprotein mediates viral attachment to the CD4 receptor and chemokine coreceptor.

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Educational objective:
R5 strains (macrophage-tropic) of HIV attach to the host CD4 receptor and CCR5 chemokine coreceptor; CCR5 inhibitors such as maraviroc can be used in the treatment of R5 virus. X4 strains (T lymphotropic) of HIV bind to the CD4 receptor and CXCR4 chemokine receptor; X4 virus cannot be treated with CCR5 inhibitors.

Pharmacology	Infectious Diseases	HIV
Subject	System	Topic

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The antiviral activity of a guanosine derivative is tested by examining cells infected with different viruses for characteristic abnormal changes in cell morphology due to the viruses. These changes are known as the cytopathic effect (CPE). In the presence of significant antiviral activity, CPE will be inhibited. The following results are obtained from the study:

	CPE without antiviral agent	CPE with antiviral agent
Herpes simplex virus 1	+++	–
Herpes simplex virus 2	+++	–
Epstein-Barr virus	+++	++
Varicella zoster virus	+++	–
Cytomegalovirus	+++	++

A difference in which of the following best explains the variation in susceptibility of the various viruses to this specific antiviral agent?

- A. DNA polymerase structure
- B. Drug degradation rate
- C. Drug phosphorylation rate
- D. Viral capsid protein composition
- E. Viral protease activity

Submit

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Varicella zoster virus	+++	–
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A difference in which of the following best explains the variation in susceptibility of the various viruses to this specific antiviral agent?

A. DNA polymerase structure (23%)
B. Drug degradation rate (1%)
✓ C. Drug phosphorylation rate (43%)
D. Viral capsid protein composition (19%)
E. Viral protease activity (11%)

Omitted
Correct answer
C

43%
Answered correctly

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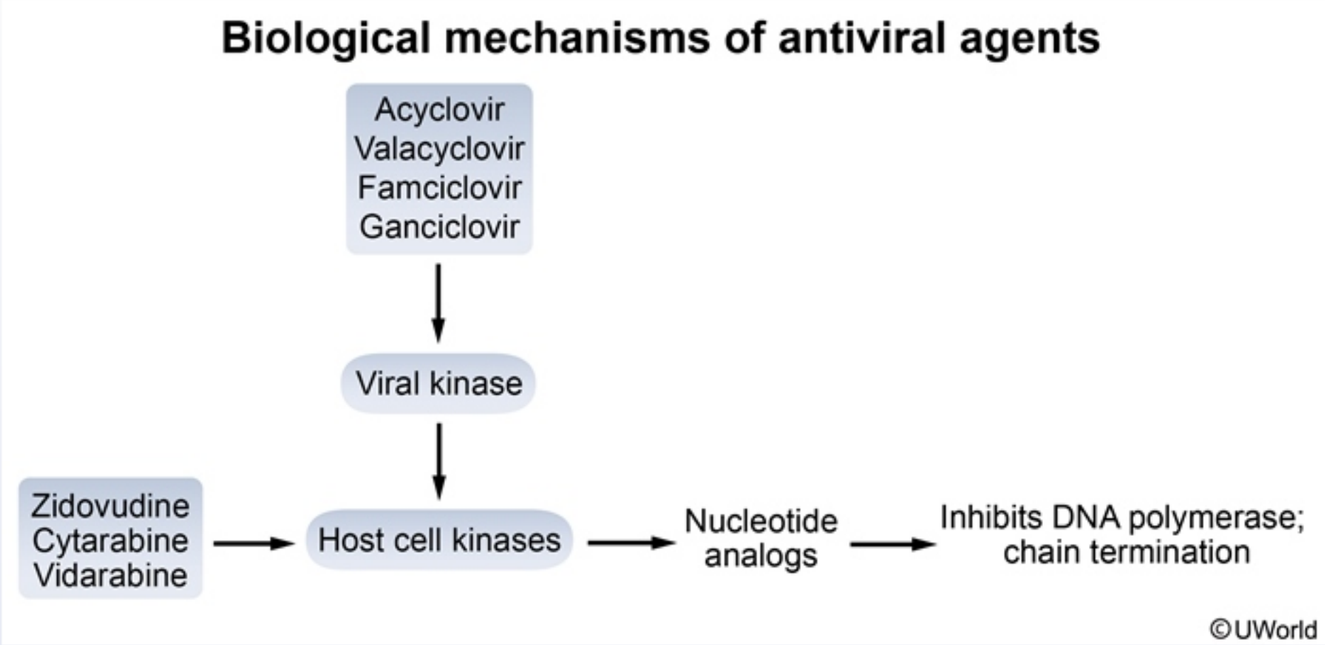
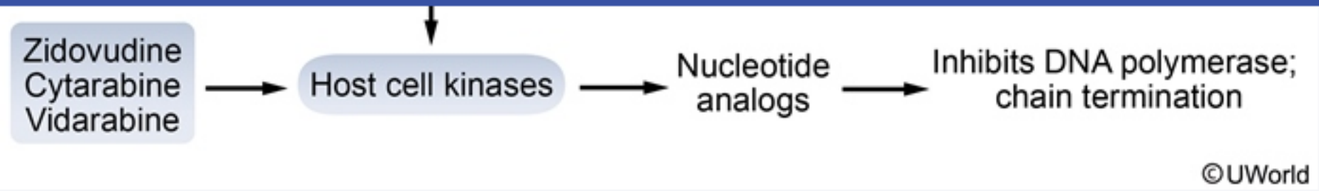


The drug described in this study demonstrates significant antiviral activity (cytopathic effect) against herpes simplex virus type 1 (HSV 1), HSV 2, and varicella zoster virus (VZV) but has weak activity against Epstein-Barr virus (EBV) and cytomegalovirus (CMV). This agent is most likely **acyclovir**, a guanosine analog. Once acyclovir enters the HSV-infected host cell, it is **phosphorylated** to acyclovir monophosphate, principally via a **virally**-encoded thymidine kinase (TK). This is the **rate-limiting** step in acyclovir activation. Acyclovir monophosphate is then phosphorylated by **cellular** enzymes into the active triphosphate form, which impairs viral DNA polymerase-mediated replication of HSV.

EBV and CMV do not produce the same TK as HSV and VZV. As a result, EBV- or CMV-infected cells cannot easily convert acyclovir into its pharmacologically active form. At very high intracellular concentrations of acyclovir, some of the drug appears to be activated by unidentified cellular phosphorylating enzymes, which may explain the partial susceptibility of EBV and CMV to higher acyclovir doses. The partial activity of acyclovir against CMV may also be mediated by inhibited synthesis of a virus-specific polypeptide.

(Choices A, B, and E) Mutations in viral DNA polymerase can lead to acyclovir resistance, but differences in TK are the best explanation for the observed results. Drug degradation rate and viral protease activity are not responsible for differences in viral susceptibility to acyclovir.



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(Choice D) TK is an enzyme produced in infected cells, but it is not present in the capsid.

Educational objective:
Monophosphorylation of acyclovir by a viral thymidine kinase is the first (and rate-limiting) step in conversion of acyclovir to its active triphosphate form. Acyclovir and related drugs (eg, famciclovir, valaciclovir) are more effective against herpes simplex virus and varicella zoster virus than cytomegalovirus and Epstein-Barr virus.

Pharmacology	Infectious Diseases	Acyclovir
Subject	System	Topic

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A 43-year-old man comes to the emergency department due to fever, chest pain, and hemoptysis. He has a history of a hematologic malignancy for which he recently underwent a cycle of chemotherapy. Laboratory studies show neutropenia due to the chemotherapeutic agents. A nodule with surrounding hypoattenuation is revealed on chest CT. Galactomannan and beta-D-glucan assays are elevated. Sputum cultures grow *Aspergillus*. The patient is placed on intravenous amphotericin B. During the infusion, he develops headaches, rigors, and hypotension. Over the next few days, there is a decline in renal function attributed to amphotericin. These toxic effects are likely due to binding of the antifungal agent to which of the following?

A. Cell membrane cholesterol

B. Cytochrome P450

C. Microtubular proteins

D. Mitochondrial enzymes

E. Ribosomal subunit

Submit

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- ✓ A. Cell membrane cholesterol (75%)
- B. Cytochrome P450 (7%)
- C. Microtubular proteins (9%)
- D. Mitochondrial enzymes (4%)
- E. Ribosomal subunit (3%)

Omitted
Correct answer
A

75%
Answered correctly

02 secs
Time Spent

04/06/2020
Last Updated

Explanation

This patient with febrile neutropenia following chemotherapy has invasive aspergillosis (fever, chest pain, hemoptysis, chest imaging showing nodule with hypoattenuation consistent with "halo sign"). **Amphotericin B** is a mainstay of treatment for many systemic mycoses. It preferentially binds the **ergosterol** of fungal cell membranes, leading to fungal cell lysis. This drug is relatively selective as it has a higher affinity for ergosterol (in fungal membranes) than for cholesterol (in human cell membranes). However, it binds **cholesterol** to a degree, which explains a large number

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Amphotericin B is often administered intravenously. Its main toxicities include the following:

- **Acute infusion-related reactions**, such as fever, chills, rigors, and hypotension, can occur. These are common and are seen most frequently during initial infusions (often diminish with subsequent infusions). Premedication with antipyretics and antihistamines can lessen the severity of these effects.
- **Dose-dependent nephrotoxicity** can result from a drug-induced decrease in the glomerular filtration rate. Permanent loss of renal function is thought to be related to the cumulative total dose. Renal function (eg, creatinine) should be closely monitored in patients undergoing treatment with amphotericin. Concomitant administration of other nephrotoxic drugs (eg, aminoglycosides, cyclosporine) should be avoided.
- Significant **electrolyte abnormalities** (hypomagnesemia and hypokalemia) can develop. These effects occur in the majority of patients within the first week of therapy. Electrolytes should be monitored daily and replaced as needed.
- **Anemia** occurs due to suppression of renal erythropoietin synthesis. This effect may be severe in patients with HIV who are taking zidovudine (which also suppresses bone marrow function).
- **Thrombophlebitis** can be seen at the site of injection.

(Choice B) Triazole antifungals (eg, fluconazole, itraconazole) inhibit cytochrome P450 enzymes, suppressing the metabolism of many other medications. This effect explains the myriad drug interactions of this group of antifungal agents.

(Choice C) Binding of microtubular proteins is the mechanism of griseofulvin, which is effective against dermatophytes only.

(Choices D and E) Amphotericin B does not interact with ribosomal subunits or mitochondrial enzymes.

Educational objective:
Amphotericin B binds the ergosterol of fungal cell membranes to exert its antifungal effects. However, it also binds cholesterol to some degree, causing toxicity to human tissues. The most important adverse effects of amphotericin B are nephrotoxicity, hypokalemia, and hypomagnesemia.

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Pharmacology	Infectious Diseases	Aspergillosis
Subject	System	Topic

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A 29-year-old woman comes to the office with malaise, fever, and extremely painful genital lesions. She has never had such symptoms before. She is sexually active with a new partner. On examination, the patient has several tiny, thin-walled vesicles on an erythematous base and exquisitely tender, shallow ulcers on the labia. Tender inguinal lymphadenopathy is present. Tzanck smear of the genital lesions shows multinucleated giant cells. A drug is prescribed that can be used to manage this acute episode and prevent future episodes of this patient's condition. This drug most likely works by which of the following mechanisms?

- A. Incorporation into newly replicating viral DNA
- B. Inhibition of viral protease activity
- C. Inhibition of virion release from infected cells
- D. Prevention of viral entry into the target cells
- E. Upregulation of interferon synthesis in infected cells

Submit

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- ✓ A. Incorporation into newly replicating viral DNA (69%)
- B. Inhibition of viral protease activity (13%)
- C. Inhibition of virion release from infected cells (8%)
- D. Prevention of viral entry into the target cells (6%)
- E. Upregulation of interferon synthesis in infected cells (2%)

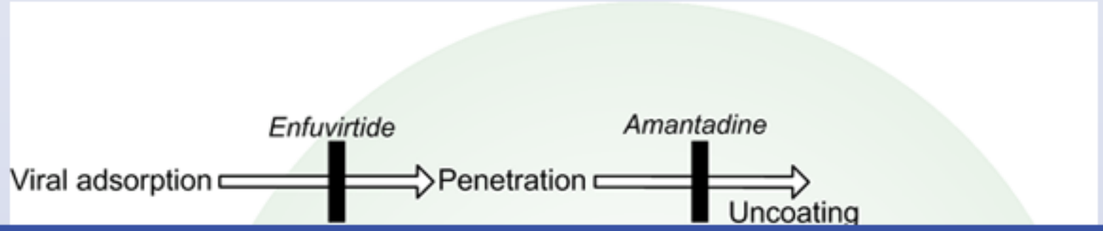
Omitted
Correct answer
A

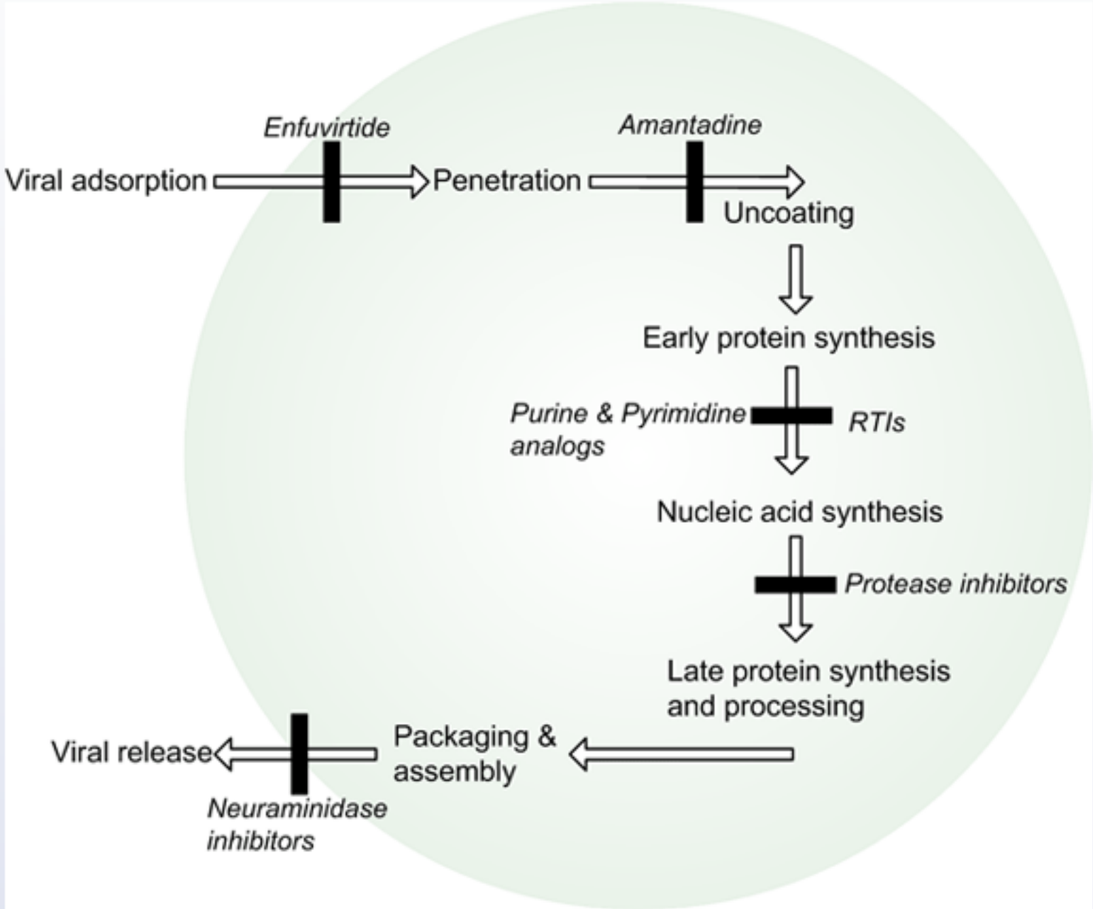
69%
Answered correctly

02 secs
Time Spent

02/08/2020
Last Updated

Explanation





This patient's new genital rash and positive Tzanck smear are consistent with a **primary genital herpes** simplex virus (HSV) infection, likely due to HSV-2. **Antiviral drugs** for the treatment of primary genital herpes include acyclovir, valacyclovir (acyclovir prodrug with better oral bioavailability), and famciclovir. Acyclovir treatment during a primary episode can reduce duration of viral shedding, time to lesional healing, constitutional symptoms, and local pain. Chronic daily suppressive therapy (lower dose) can be used in patients who have recurrent episodes.

In infected host cells, acyclovir (a **nucleoside analog**) is converted into acyclovir monophosphate principally via **virus-encoded** thymidine kinase. Cellular enzymes then convert the monophosphate into acyclovir triphosphate, which competes with deoxyguanosine triphosphate for

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

This patient's new genital rash and positive Tzanck smear are consistent with a **primary genital herpes** simplex virus (HSV) infection, likely due to HSV-2. **Antiviral drugs** for the treatment of primary genital herpes include acyclovir, valacyclovir (acyclovir prodrug with better oral bioavailability), and famciclovir. Acyclovir treatment during a primary episode can reduce duration of viral shedding, time to lesional healing, constitutional symptoms, and local pain. Chronic daily suppressive therapy (lower dose) can be used in patients who have recurrent episodes.

In infected host cells, acyclovir (a **nucleoside analog**) is converted into acyclovir monophosphate principally via **virus-encoded** thymidine kinase. Cellular enzymes then convert the monophosphate into acyclovir triphosphate, which competes with deoxyguanosine triphosphate for viral DNA polymerase. When acyclovir triphosphate becomes incorporated into the replicating viral DNA chain, viral DNA synthesis is terminated.

Acyclovir does not significantly impact uninfected cells in vitro as uptake into these cells is poor, phosphorylation in the absence of viral thymidine kinase is minimal, and cellular α-DNA polymerase has significantly less affinity for acyclovir triphosphate than does viral DNA polymerase.

(Choice B) Inhibition of viral protease activity is the mechanism of action for drugs such as indinavir, an antiretroviral used in HIV treatment.

(Choice C) Prevention of virion release from infected cells is the mechanism of action for drugs such as neuraminidase inhibitors (eg, oseltamivir), which are used in the early treatment of influenza.

(Choice D) Drugs such as enfuvirtide and maraviroc, antiretrovirals used in HIV treatment, prevent viral entry into the target cells. Docosanol, a topical agent that prevents viral entry, is sometimes used for herpes labialis, not genital HSV.

(Choice E) Upregulation of interferon synthesis in infected cells is accomplished by many interleukins.

Educational objective:
Antiviral drugs currently recommended for the treatment of primary genital herpes include the nucleoside analogs (eg, acyclovir). These are incorporated into newly replicating viral DNA and ultimately terminate viral DNA chain synthesis.

Pharmacology	Infectious Diseases	Acyclovir
Subject	System	Topic

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A mother brings her 4-year-old son to see you because he has been experiencing decreased appetite, fever, and right-sided ear discharge for the past 24 hours. His past medical history is significant for three episodes of otitis media over the last year. You prescribe amoxicillin. Adding clavulanic acid to this treatment regimen would serve which of the following purposes?

A. Kill bacteria via a different mechanism of action

B. Decrease amoxicillin cleavage by immune cells

C. Decrease amoxicillin cleavage by bacterial cells

D. Slow liver metabolism of amoxicillin

E. Decrease renal clearance of amoxicillin

Submit

A mother brings her 4-year-old son to see you because he has been experiencing decreased appetite, fever, and right-sided ear discharge for the past 24 hours. His past medical history is significant for three episodes of otitis media over the last year. You prescribe amoxicillin. Adding clavulanic acid to this treatment regimen would serve which of the following purposes?

A. Kill bacteria via a different mechanism of action (4%)

B. Decrease amoxicillin cleavage by immune cells (1%)

✓ C. Decrease amoxicillin cleavage by bacterial cells (86%)

D. Slow liver metabolism of amoxicillin (3%)

E. Decrease renal clearance of amoxicillin (4%)

Omitted
Correct answer
C

86%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

Certain strains of bacteria produce the beta-lactamase enzyme, which hydrolyzes the beta-lactam ring of penicillin family antibiotics rendering them ineffective. To help prevent this effect, beta-lactamase inhibiting compounds have been developed. The beta-lactamase inhibitors include clavulanic acid, sulbactam and tazobactam. Concurrent administration of a beta-lactamase inhibitor with a beta-lactamase susceptible antibiotic allows that antibiotic to retain its efficacy against the offending bacterium. For example, giving clavulanate together with amoxicillin expands amoxicillin's spectrum of activity to include strains of beta-lactamase synthesizing bacteria which would otherwise have been resistant to amoxicillin alone.

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Explanation

Certain strains of bacteria produce the beta-lactamase enzyme, which hydrolyzes the beta-lactam ring of penicillin family antibiotics rendering them ineffective. To help prevent this effect, beta-lactamase inhibiting compounds have been developed. The beta-lactamase inhibitors include clavulanic acid, sulbactam and tazobactam. Concurrent administration of a beta-lactamase inhibitor with a beta-lactamase susceptible antibiotic allows that antibiotic to retain its efficacy against the offending bacterium. For example, giving clavulanate together with amoxicillin expands amoxicillin's spectrum of activity to include strains of beta-lactamase synthesizing bacteria which would otherwise have been resistant to amoxicillin alone.

(Choice A) Clavulanic acid has negligible intrinsic antibacterial activity.

(Choice B) Immune cells do not produce beta-lactamases.

(Choice D) Clavulanic acid has no effect on the biotransformation of amoxicillin in the liver. Moreover amoxicillin undergoes enterohepatic recirculation and is excreted primarily in unchanged form in the urine.

(Choice E) Probenecid is a compound that decreases the renal clearance of penicillins by inhibiting the tubular organic acid secretion system. This agent has been utilized to prolong the action of penicillin in some settings.

Educational Objective:
Clavulanic acid, sulbactam and tazobactam are beta-lactamase inhibitors. Concurrent administration of clavulanate with amoxicillin expands amoxicillin's spectrum of activity to include strains of β-lactamase synthesizing bacteria that are resistant to amoxicillin alone.

Pharmacology	Infectious Diseases	Penicillin
Subject	System	Topic

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A 26-year-old man is being evaluated for recurrent boils and skin abscesses. Anterior nares swab culture is performed to determine colonization by the culprit bacteria, which yields gram-positive cocci in clusters. The bacteria are able to grow in a media containing oxacillin. PCR testing reveals the pathogen has acquired the *mecA* gene. These bacteria are most likely to be resistant to which of the following antibiotics?

- A. Cefazolin
- B. Clindamycin
- C. Doxycycline
- D. Trimethoprim-sulfamethoxazole
- E. Vancomycin

Submit

A 26-year-old man is being evaluated for recurrent boils and skin abscesses. Anterior nares swab culture is performed to determine colonization by the culprit bacteria, which yields gram-positive cocci in clusters. The bacteria are able to grow in a media containing oxacillin. PCR testing reveals the pathogen has acquired the *mecA* gene. These bacteria are most likely to be resistant to which of the following antibiotics?

- ✓ A. Cefazolin (60%)
- B. Clindamycin (4%)
- C. Doxycycline (3%)
- D. Trimethoprim-sulfamethoxazole (1%)
- E. Vancomycin (29%)

Omitted
Correct answer
A

60%
Answered correctly

02 secs
Time Spent

06/13/2020
Last Updated

Explanation

This patient with recurrent boils and skin abscesses is likely colonized with ***Staphylococcus aureus***, a gram-positive cocci that grows in clusters. Methicillin-resistant strains are able to grow in the presence of oxacillin due to the acquisition of a mobile genetic element that contains the ***mecA* gene**, which encodes for **penicillin-binding protein (PBP) 2a**. PBPs catalyze peptidoglycan cross-linking during cell wall synthesis; they are the target of beta-lactam medications, which bind to and irreversibly destroy the enzyme. Unlike other PBPs, PBP 2a has a **low affinity for beta-lactams** and continues to cross-link peptidoglycan in the presence of oxacillin, methicillin, cephalosporins (eg, **cefazolin**), and other beta-lactam medications.

Therefore, treatment of methicillin-resistant *S aureus* (MRSA) generally requires the use of a non–beta-lactam drug. Common medications for

Omitted
Correct answer
A

60%
Answered correctly

02 secs
Time Spent

06/13/2020
Last Updated

Explanation

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Therefore, treatment of methicillin-resistant *S aureus* (MRSA) generally requires the use of a non–beta-lactam drug. Common medications for MRSA include trimethoprim-sulfamethoxazole (inhibits 2 steps in folate synthesis), clindamycin (inhibits bacterial protein synthesis by binding to the 50s ribosomal subunit), doxycycline (inhibits protein synthesis by binding to the 30s ribosomal subunit), or vancomycin (inhibits integration of peptidoglycan subunits) **(Choices B, C, D, and E)**.

Educational objective:
Methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant to most beta-lactam medications (eg, oxacillin, methicillin, cephalosporins) due to the acquisition of a mobile genetic element that contains the *mecA* gene. This gene encodes for a specialized penicillin-binding protein that has low affinity for beta-lactam antibiotics. Treatment of MRSA therefore requires a non–beta-lactam medication such as trimethoprim-sulfamethoxazole, clindamycin, doxycycline, or vancomycin.

Pharmacology	Infectious Diseases	Antibiotic resistance
Subject	System	Topic

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A 50-year-old woman comes to the emergency department due to fever and abdominal pain. The patient has a history of type 2 diabetes mellitus. Her temperature is 38.3 C (101 F). Abdominal examination is notable for right upper quadrant tenderness to palpation that is worsened by deep inspiration. Laboratory studies show leukocytosis. An ultrasound of the abdomen reveals multiple gallstones and gallbladder wall thickening with pericholecystic fluid. Blood cultures are drawn, and surgical consultation is requested. The patient is initiated on intravenous piperacillin combined with tazobactam. Which of the following is the most likely reason to use this drug combination in this patient?

A. Decrease bacterial inactivation of piperacillin
B. Decrease renal clearance of piperacillin
C. Enhance bacterial penetration of piperacillin
D. Increase bioavailability of piperacillin
E. Provide additive antimicrobial activity

Submit

A 50-year-old woman comes to the emergency department due to fever and abdominal pain. The patient has a history of type 2 diabetes mellitus. Her temperature is 38.3 C (101 F). Abdominal examination is notable for right upper quadrant tenderness to palpation that is worsened by deep inspiration. Laboratory studies show leukocytosis. An ultrasound of the abdomen reveals multiple gallstones and gallbladder wall thickening with pericholecystic fluid. Blood cultures are drawn, and surgical consultation is requested. The patient is initiated on intravenous piperacillin combined with tazobactam. Which of the following is the most likely reason to use this drug combination in this patient?

- ✓ A. Decrease bacterial inactivation of piperacillin (79%)
- B. Decrease renal clearance of piperacillin (2%)
- C. Enhance bacterial penetration of piperacillin (8%)
- D. Increase bioavailability of piperacillin (2%)
- E. Provide additive antimicrobial activity (6%)

Omitted
Correct answer
A

79%
Answered correctly

02 secs
Time Spent

02/14/2020
Last Updated

Explanation

This patient's fever, leukocytosis, right upper quadrant pain with positive Murphy sign, and ultrasound findings (eg, gallstones, wall thickening, pericholecystic fluid) indicate **acute cholecystitis**. Antibiotic therapy is often administered to prevent secondary infection (eg, *Escherichia coli, Klebsiella*) due to biliary stasis, particularly in patients who have diabetes mellitus or immunodeficiency.

The penicillin family of antibiotics (eg, piperacillin) contains a **beta-lactam ring**, which inhibits peptidoglycan cross-linking and causes bacterial cell wall disruptions. Resistance is often due to **beta-lactamase**, a bacterial enzyme that hydrolyzes and inactivates the beta-lactam ring. The

This patient's fever, leukocytosis, right upper quadrant pain with positive Murphy sign, and ultrasound findings (eg, gallstones, wall thickening, pericholecystic fluid) indicate **acute cholecystitis**. Antibiotic therapy is often administered to prevent secondary infection (eg, *Escherichia coli, Klebsiella*) due to biliary stasis, particularly in patients who have diabetes mellitus or immunodeficiency.

The penicillin family of antibiotics (eg, piperacillin) contains a **beta-lactam ring**, which inhibits peptidoglycan cross-linking and causes bacterial cell wall disruptions. Resistance is often due to **beta-lactamase**, a bacterial enzyme that hydrolyzes and inactivates the beta-lactam ring. The coadministration of a **beta-lactamase inhibitor** such as tazobactam prevents beta-lactamase producing organisms from inactivating penicillins, which extends their spectrum of activity (broadens the range of microbes that can be treated).

Some penicillin-derivative antibiotics (eg, late-generation cephalosporins, carbapenems) have beta-lactam rings with additional chemical components, which make them partially or completely resistant to beta-lactamases.

(Choice B) Probenecid, a uricosuric agent used for hyperuricemia with gout, blocks the renal tubular excretion of penicillins and cephalosporins and is sometimes used to increase their serum level or prolong their half-life.

(Choice C) Aminoglycosides inhibit bacterial protein synthesis by blocking the 30S ribosomal subunit. Penicillins are often coadministered with aminoglycosides to aid in their entry into the cell (penicillins disrupt the cell wall, which allow aminoglycosides to penetrate the bacteria).

(Choice D) Piperacillin is always administered intravenously so bioavailability is 100%. Tazobactam inhibits beta-lactamase; it does not alter piperacillin metabolism or excretion.

(Choice E) Additive antimicrobial activity occurs when 2 different antibiotic classes are used in combination, such as a fluoroquinolone (DNA gyrase inhibitor) with vancomycin (cell wall synthesis inhibitor). Beta-lactamase inhibitors block an enzyme that destroys penicillins; they do not independently provide antimicrobial activity so they are always used in combination with penicillin-class agents.

Educational objective:
Beta-lactamase inhibitors (eg, clavulanic acid, sulbactam, tazobactam) prevent beta-lactamase from inactivating penicillin class drugs, which extends the spectrum of their activity.

Pharmacology	Infectious Diseases	Penicillin
Subject	System	Topic

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A 32-year-old woman comes to the physician for a health maintenance examination. She has been well and has no specific complaints. She eats a well-balanced diet and exercises on a stationary bicycle 3 days a week. She works as a nursing assistant at a local hospital. Review of her records shows that she is due for her annual influenza vaccination. Prior to administration of the vaccine, her skin is disinfected with 70% isopropanol. Which of the following mechanisms is most likely responsible for the antiseptic properties of isopropanol?

A. Coagulation of the cytoplasm
B. Cross-linking of proteins
C. Disruption of cell membranes
D. Halogenation of proteins
E. Production of free radicals

Submit

A 32-year-old woman comes to the physician for a health maintenance examination. She has been well and has no specific complaints. She eats a well-balanced diet and exercises on a stationary bicycle 3 days a week. She works as a nursing assistant at a local hospital. Review of her records shows that she is due for her annual influenza vaccination. Prior to administration of the vaccine, her skin is disinfected with 70% isopropanol. Which of the following mechanisms is most likely responsible for the antiseptic properties of isopropanol?

- A. Coagulation of the cytoplasm (2%)
- B. Cross-linking of proteins (3%)
- ✓ C. Disruption of cell membranes (77%)
- D. Halogenation of proteins (4%)
- E. Production of free radicals (11%)

Omitted
Correct answer
C

77%
Answered correctly

01 sec
Time Spent

07/02/2020
Last Updated

Explanation

Commonly used clinical disinfectants

Agent	Mechanism	Sporicidal
Alcohols	Disruption of cell membranes	

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

Commonly used clinical disinfectants

Agent	Mechanism	Sporicidal
Alcohols (isopropanol, ethanol)	Disruption of cell membranes Denaturation of proteins	No
Chlorhexidine	Disruption of cell membranes Coagulation of cytoplasm	No
Hydrogen peroxide	Produces destructive free radicals that oxidize cellular components	Yes
Iodine	Halogenation of proteins & nucleic acids	Yes

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Alcohols, including ethanol and isopropanol, are widely used as disinfecting agents in the health care setting. They are commonly used to clean the skin before immunization or venipuncture and to disinfect external surfaces of equipment. They function by disorganizing the lipid structure in membranes, causing them to be leaky, and by denaturing cellular proteins. Alcohols require the presence of water for maximal activity and are most effective at 60%-90% concentration. They are rapidly bactericidal and also tuberculocidal, fungicidal, and virucidal, but do not destroy bacterial spores.

(Choice A) Chlorhexidine works by destabilizing cell membranes and coagulating intracellular constituents. In combination with 70% alcohol, it is the antiseptic of choice for many surgical and percutaneous procedures. Its use is contraindicated in neurologic, otologic, and ophthalmologic procedures due to neurotoxicity.

(Choice B) Formaldehyde and glutaraldehyde function by alkylating and cross-linking DNA and proteins. They are most commonly used for sterilization of hospital instruments that cannot withstand autoclave temperatures.

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Alcohols, including ethanol and isopropanol, are widely used as disinfecting agents in the health care setting. They are commonly used to clean the skin before immunization or venipuncture and to disinfect external surfaces of equipment. They function by disorganizing the lipid structure in membranes, causing them to be leaky, and by denaturing cellular proteins. Alcohols require the presence of water for maximal activity and are most effective at 60%-90% concentration. They are rapidly bactericidal and also tuberculocidal, fungicidal, and virucidal, but do not destroy bacterial spores.

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(Choice B) Formaldehyde and glutaraldehyde function by alkylating and cross-linking DNA and proteins. They are most commonly used for sterilization of hospital instruments that cannot withstand autoclave temperatures.

(Choice D) Iodine causes halogenation of proteins and DNA. Solutions containing iodine are frequently used for antisepsis in surgical and percutaneous procedures. However, they are less effective than chlorhexidine-alcohol and cause more skin irritation and toxicity.

(Choice E) Hydrogen peroxide functions as an oxidant by producing hydroxyl free radicals that attack cellular components. It is excellent at disinfecting inanimate objects but is less effective when used on organic materials. Hydrogen peroxide is often used for skin cleansing and wound debridement due to its effervescent quality.

Educational objective:
Alcohols function by disorganizing the lipid structure in membranes, causing them to be leaky, and by denaturing cellular proteins. They are bactericidal, tuberculocidal, fungicidal, and virucidal, but do not destroy bacterial spores.

References

- Antiseptics and disinfectants: activity, action, and resistance.

Pharmacology	Infectious Diseases	Infection control
Subject	System	Topic

A 42-year-old man comes to the emergency department due to fever, abdominal pain, and explosive diarrhea. He has a history of HIV but has not been taking any medications. BMI is 18.2 kg/m^2. Abdominal examination is notable for right-sided tenderness to palpation. Laboratory results show a CD4 cell count of 38/mm^3, leukopenia, and thrombocytopenia. A CT scan of the abdomen reveals colitis. Colonoscopy reveals areas of erosions and ulcerations; pathology demonstrates cells with viral intranuclear and intracytoplasmic inclusions. Antiviral therapy is initiated to treat the colitis with an intravenous agent that does not require intracellular activation and is known to bind in vitro with viral-encoded enzymes such as DNA polymerase, RNA polymerase, and reverse transcriptase. Which of the following agents did this patient most likely receive?

- A. Acyclovir
- B. Foscarnet
- C. Ganciclovir
- D. Lamivudine
- E. Oseltamivir
- F. Saquinavir
- G. Sofosbuvir

Submit

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- A. Acyclovir (3%)
- ✓ B. Foscarnet (56%)
- C. Ganciclovir (16%)
- D. Lamivudine (13%)
- E. Oseltamivir (3%)
- F. Saquinavir (3%)
- G. Sofosbuvir (3%)

Omitted
Correct answer
B

56%
Answered correctly

02 secs
Time Spent

04/06/2020
Last Updated

Explanation

This patient with HIV likely has cytomegalovirus (CMV) colitis (intranuclear and intracytoplasmic inclusions), which, in some patients (eg, with

This patient with HIV likely has cytomegalovirus (CMV) colitis (intranuclear and intracytoplasmic inclusions), which, in some patients (eg, with ganciclovir resistance or refractory thrombocytopenia), is treated with foscarnet. **Foscarnet** is a pyrophosphate analog that does **not** require intracellular activation. It directly inhibits both DNA polymerase in herpesvirus and reverse transcriptase in HIV. Foscarnet must be administered intravenously. In addition to treating ganciclovir-resistant CMV infections, foscarnet is useful in patients who have acyclovir-resistant herpesvirus infections. **Ganciclovir**, a guanine nucleoside analogue structurally similar to acyclovir, is often used for CMV infections. However, it requires intracellular conversion by a virally encoded kinase and then by cellular kinases **(Choice C)**.

(Choice A) Acyclovir is a nucleoside analog that must be converted intracellularly to its monophosphate form by a virally encoded thymidine kinase. Cellular kinases convert the monophosphate form into a triphosphate form, which inhibits herpesvirus DNA polymerase-mediated replication.

(Choice D) Lamivudine is a cytosine analog classified as a nucleoside reverse transcriptase inhibitor. It must be phosphorylated to its active form, lamivudine triphosphate, by intracellular kinases. Lamivudine inhibits HIV reverse transcription through viral DNA chain termination.

(Choices E and F) Oseltamivir and saquinavir do not require intracellular activation but are not used for CMV infection. Oseltamivir is a sialic acid analogue inhibitor of influenza A and B virus neuraminidase. Saquinavir is an HIV protease inhibitor that prevents the cleavage of polyprotein precursors necessary for the generation of functional viral proteins.

(Choice G) Sofosbuvir inhibits nonstructural protein 5B (NS5B), an RNA-dependent RNA polymerase needed for hepatitis C virus replication. It requires intracellular activation.

Educational objective:
Of all the antiviral agents that bind and inhibit DNA polymerase in herpesvirus and reverse transcriptase in HIV, the pyrophosphate analog foscarnet is one of few that do not require intracellular activation by viral or cellular kinases.

Pharmacology	Infectious Diseases	Cytomegalovirus
Subject	System	Topic

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A 19-year-old woman comes to the office due to 2 days of dysuria, urinary frequency, and urgency. The symptoms began a day after having sexual intercourse with her boyfriend. The patient has no fever, flank pain, nausea, or vomiting. She has no chronic medical conditions and no known drug allergies. Vital signs are within normal limits. Examination shows mild suprapubic tenderness. Urinalysis reveals many bacteria and white blood cells/hpf. Which of the following is the most appropriate pharmacotherapy for this patient?

A. Azithromycin
B. Doxycycline
C. Fluconazole
D. Metronidazole
E. Trimethoprim-sulfamethoxazole

Submit

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- A. Azithromycin (12%)
- B. Doxycycline (6%)
- C. Fluconazole (0%)
- D. Metronidazole (6%)
- ✓ E. Trimethoprim-sulfamethoxazole (74%)

Omitted
Correct answer
E

74%
Answered correctly

02 secs
Time Spent

02/04/2020
Last Updated

Explanation

This patient's acute dysuria, urinary frequency/urgency, suprapubic tenderness, and pyuria/bacteriuria indicate **acute simple cystitis**. Women are at greater risk than men due to the short distance between the anus and vaginal introitus, which allows enteric bacteria to contaminate the urethra and ascend into the bladder. **Recent sexual intercourse** is the single greatest risk factor in otherwise healthy women.

Most cases of acute simple cystitis are caused by the enteric bacteria ***Escherichia coli***. However, *Klebsiella pneumoniae*, *Proteus mirabilis,* and *Staphylococcus saprophyticus* are also frequently isolated. Patients with no risk factors for resistant bacteria (eg, recent inpatient hospitalization or antibiotic use) are generally treated empirically with 3-6 days of nitrofurantoin or **trimethoprim-sulfamethoxazole** (TMP-SMX) due to their

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This patient's acute dysuria, urinary frequency/urgency, suprapubic tenderness, and pyuria/bacteriuria indicate **acute simple cystitis**. Women are at greater risk than men due to the short distance between the anus and vaginal introitus, which allows enteric bacteria to contaminate the urethra and ascend into the bladder. **Recent sexual intercourse** is the single greatest risk factor in otherwise healthy women.

Most cases of acute simple cystitis are caused by the enteric bacteria ***Escherichia coli***. However, *Klebsiella pneumoniae*, *Proteus mirabilis,* and *Staphylococcus saprophyticus* are also frequently isolated. Patients with no risk factors for resistant bacteria (eg, recent inpatient hospitalization or antibiotic use) are generally treated empirically with 3-6 days of nitrofurantoin or **trimethoprim-sulfamethoxazole** (TMP-SMX) due to their excellent efficacy and low risk of side effects.

(Choices A and B) Azithromycin and doxycycline treat *Chlamydia trachomatous* infections of the urogenital tract. Most cases of chlamydia are asymptomatic, but some patients have dysuria and urinary frequency. Although urinalysis will reveal pyuria, no bacteria would be seen on urinary Gram stain because *C trachomatous* has no cell wall. Neither azithromycin nor doxycycline adequately treats enteric, gram-negative pathogens; therefore, neither is typically used for acute simple cystitis.

(Choice C) Fluconazole is often used to treat vaginal candidiasis, which can cause dysuria and is often linked to vaginal intercourse. However, most patients also have vaginal itching and soreness. The presence of urinary frequency, urgency, and pyuria/bacteriuria makes bacterial cystitis more likely.

(Choice D) Metronidazole can treat *Trichomonas vaginalis*, a flagellated protozoan that is transmitted during sexual intercourse. Women infected with trichomonas often have dysuria and frequency, but most also have a purulent, malodourous vaginal discharge. The presence of pyuria/bacteriuria on urinalysis makes acute bacterial cystitis more likely.

Educational objective:
Acute simple cystitis often occurs in young, otherwise healthy women, particularly following sexual intercourse. Common manifestations include dysuria, urinary frequency/urgency, and urinalysis evidence of pyuria/bacteriuria. Empiric treatment with nitrofurantoin or trimethoprim-sulfamethoxazole is typically curative.

Pharmacology	Infectious Diseases	Urinary tract infection
Subject	System	Topic

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A 12-year-old boy is brought to the emergency department due to a skin infection. Temperature is 38.4 C (101.1 F). Physical examination shows an area of erythema, warmth, and tenderness on his right distal leg. Laboratory results are notable for leukocytosis. The patient is started on intravenous nafcillin. Two days later, he shows limited response to antibiotic therapy. Light microscopy of pus obtained from the site shows gram-positive cocci in clusters, and sensitivity testing demonstrates little response to nafcillin but good response to vancomycin. Which of the following is the most likely explanation for nafcillin treatment failure in this patient?

A. Active drug transport out of the cell

B. Enzymatic degradation of the drug

C. Mutation in DNA gyrase

D. Mutation in RNA polymerase

E. Poor interaction with binding proteins

Submit

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- A. Active drug transport out of the cell (3%)
- B. Enzymatic degradation of the drug (20%)
- C. Mutation in DNA gyrase (1%)
- D. Mutation in RNA polymerase (1%)
- ✓ E. Poor interaction with binding proteins (73%)

Omitted
Correct answer
E

73%
Answered correctly

01 sec
Time Spent

02/27/2020
Last Updated

Explanation

Common antibiotic resistance mechanisms	
Penicillins	• Beta-lactamase, ESBL • Mutated PBP • Mutated porin protein

Common antibiotic resistance mechanisms	
Penicillins	• Beta-lactamase, ESBL • Mutated PBP • Mutated porin protein
Vancomycin	• Mutated peptidoglycan cell wall • Impaired influx/increased efflux
Quinolones	• Mutated DNA gyrase • Impaired influx/increased efflux
Aminoglycosides	• Aminoglycoside-modifying enzymes • Mutated ribosomal subunit protein • Mutated porin protein
Tetracyclines	• Impaired influx/increased efflux • Inactivated enzyme
Rifamycins	• Mutated RNA polymerase

ESBL = extended-spectrum beta-lactamase; PBP = penicillin-binding protein.

The presence of gram-positive cocci in clusters that do not respond to nafcillin but show sensitivity to vancomycin suggests infection with **methicillin-resistant *Staphylococcus aureus*** (MRSA). *S aureus* is a common cause of skin infections in the United States. Most skin infections are minor, but *S aureus* can cause serious infections (eg, surgical wound infections, bloodstream infections in the presence of central intravenous catheters, pneumonia).

S aureus strains that are resistant to oxacillin, nafcillin, and methicillin have been historically termed **MRSA**, but they are also resistant to all β-lactam agents, including penicillin, cephalosporins (except ceftaroline, a fifth-generation cephalosporin), and carbapenems. Methicillin (nafcillin) **resistance** is typically mediated by alterations in the structure of **penicillin-binding proteins** (PBP), the enzymes involved in cell wall synthesis. Altered PBPs, especially PBP2a, have greatly **reduced affinity** for β-lactam antimicrobial agents (except ceftaroline).

Rifamycins	• Mutated RNA polymerase

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(Choice A) Resistance to tetracycline and sulfonamides is due at least in part to a decrease in the levels of drug accumulation due to decreased uptake and/or increased efflux.

(Choice B) Approximately 95% of *S aureus* isolates in the United States produce penicillinase, which causes penicillin resistance by breaking penicillin's β-lactam ring. However, nafcillin is penicillinase-stable (along with oxacillin and methicillin).

(Choices C and D) Mutations in DNA gyrase cause resistance to quinolone antibiotics. Mutations in RNA polymerase cause resistance to rifampin.

Educational objective:
Methicillin-resistant *Staphylococcus aureus* is resistant to all β-lactam antibiotics, including beta-lactamase-resistant antibiotics, as it has an altered penicillin-binding protein that does not bind β-lactams effectively.

Pharmacology	Infectious Diseases	Antibiotic resistance
Subject	System	Topic

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A 21-year-old woman comes to the office due to burning on urination and increased urinary frequency for the past 2 days. She has no hematuria, vaginal discharge, or irritation. The patient has no other medical problems. Her temperature is 37 C (98.6 F). Physical examination reveals mild suprapubic tenderness on deep palpation; there is no costovertebral angle tenderness. Urine dipstick is positive for leukocyte esterase and nitrites. The patient is started on trimethoprim, which leads to rapid resolution of her symptoms. Which of the following drugs has the same intracellular target as the drug used to treat this patient?

A. Bacitracin
B. Imipenem
C. Methotrexate
D. Metronidazole
E. Sulfamethoxazole

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- A. Bacitracin (4%)
- B. Imipenem (2%)
- ✓ C. Methotrexate (69%)
- D. Metronidazole (2%)
- E. Sulfamethoxazole (20%)

Omitted
Correct answer
C

69%
Answered correctly

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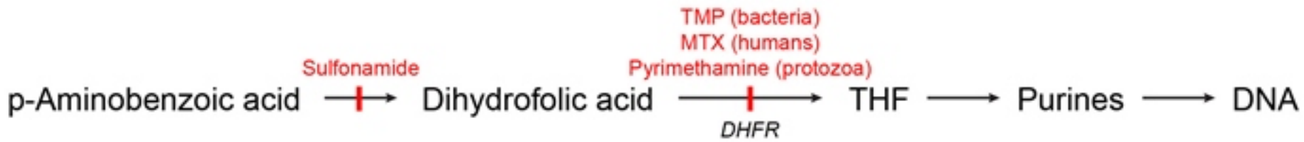
Time Spent

03/30/2020
Last Updated

Explanation

Trimethoprim-sulfamethoxazole & folic acid pathway



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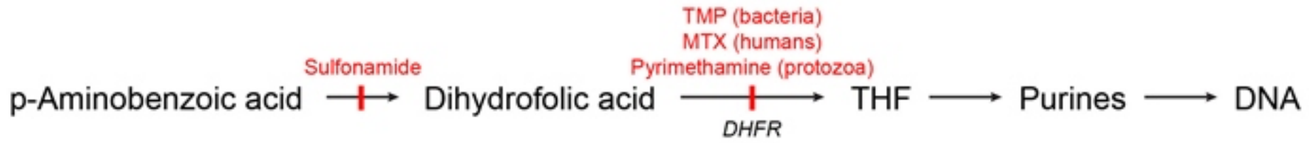
Trimethoprim-sulfamethoxazole & folic acid pathway



DHFR = dihydrofolate reductase; MTX = methotrexate; THF = tetrahydrofolic acid; TMP = trimethoprim ©UWorld

Trimethoprim (in bacteria), methotrexate (in human cells), and pyrimethamine (in some protozoa) all prevent the reduction of folic acid to tetrahydrofolate (THF) by inhibiting dihydrofolate reductase (**DHFR**). **Trimethoprim** restricts **bacterial** growth through this process and works particularly well in conjunction with the sulfonamides (eg, sulfamethoxazole), which inhibit an earlier step in the bacterial folic acid pathway (described below). The combination of trimethoprim and sulfamethoxazole produces a "sequential blockade."

Methotrexate is a folate antimetabolite that targets rapidly proliferating **human** cells by halting DNA synthesis through binding DHFR. Methotrexate is cell-cycle specific for the S phase as it prevents synthesis of purine and thymidylic acid (used for pyrimidine synthesis). **Pyrimethamine** is effective for treatment of malaria and toxoplasmosis because it inhibits **parasitic** DHFR.

(Choice A) Bacitracin prevents mucopeptide transfer into the growing cell wall, thereby inhibiting bacterial cell wall synthesis.

(Choice B) Imipenem binds to penicillin binding proteins, thereby inhibiting the final step of peptidoglycan synthesis in bacterial cell walls. Cilastatin can be used in conjunction with imipenem because it prevents renal metabolism of imipenem by competitively inhibiting dehydropeptidase on the renal tubule brush border.

(Choice D) Metronidazole binds to DNA within susceptible cells, unraveling the helical structure of DNA and breaking its strands. Protein synthesis is inhibited and the cell dies soon thereafter.

(Choice E) As a structural analog of para-aminobenzoic acid (PABA), sulfamethoxazole competes with PABA to inhibit dihydropteroate synthetase, one of the enzymes needed for dihydrofolic acid synthesis. This is an intermediate step in the formation of THF.

Educational objective:
Trimethoprim, methotrexate, and pyrimethamine inhibit dihydrofolate reductase. Trimethoprim restricts bacterial growth through this process, and works particularly well in conjunction with sulfonamide, which inhibits an earlier step in the bacterial folic acid pathway.

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Pharmacology	Infectious Diseases	Folate antimetabolites
Subject	System	Topic

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A 34-year-old man comes to the emergency department due to recurrent fevers, chills, and excessive sweating. The symptoms began a few days ago and seem to occur every 48 hours. The patient recently returned from a trip to India. Temperature is 38.6 C (101.5 F). Physical examination is otherwise unrevealing. Laboratory studies are notable for anemia and thrombocytopenia. A blood smear with Giemsa staining demonstrates red blood cell inclusions. The patient is prescribed chloroquine and primaquine. The addition of primaquine to the treatment regimen is most likely to have which of the following effects?

A. Decrease the side effects of chloroquine therapy

B. Kill blood trophozoites

C. Prevent disease relapse

D. Prevent hemolysis

E. Treat chloroquine-resistant strains

Submit

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

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- A. Decrease the side effects of chloroquine therapy (1%)
- B. Kill blood trophozoites (16%)
- ✓ C. Prevent disease relapse (46%)
- D. Prevent hemolysis (2%)
- E. Treat chloroquine-resistant strains (32%)

Omitted
Correct answer
C

46%
Answered correctly

01 sec
Time Spent

05/06/2020
Last Updated

Explanation

This patient has fever, chills, sweats, and red blood cell inclusions on Giemsa smear that developed following travel to a tropical geographic region (areas including South America, Africa, India, and Southeast Asia). Together, these findings support a diagnosis of **malaria**. Fever and sweating that occur every 48 hours (tertian malaria) are especially characteristic of *Plasmodium vivax, P ovale*, or *P falciparum* infection.

All species of malaria-causing organisms share a similar life cycle. Organisms are first inoculated into the human host by the ***Anopheles*** mosquito and then travel to the **liver**, where they infect hepatocytes and replicate. Lysis of infected hepatocytes releases **merozoites** into the

Explanation

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Chloroquine is effective in eradicating chloroquine-sensitive plasmodia from the bloodstream, but it has no activity against the latent hepatic infections established by *P vivax* and *P ovale*. **Primaquine** must be added to the regimen to completely eradicate the **hypnozoites**.

(Choice A) Retinopathy is the most serious long-term adverse effect related to chloroquine use. It occurs only rarely and is related to prolonged use. Primaquine has no influence on the occurrence of chloroquine retinopathy.

(Choices B and E) Primaquine has limited therapeutic activity against the erythrocytic forms of plasmodia, including trophozoites. Primaquine is not effective in treating chloroquine-resistant strains, which can be managed with mefloquine or quinine, among others.

(Choice D) No antimalarial agent specifically acts to prevent hemolysis. Primaquine is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency as the medication can cause hemolysis.

Educational objective:
Chloroquine is the treatment of choice for uncomplicated malaria contracted in a chloroquine-sensitive geographic region. It eliminates susceptible erythrocytic forms of all *Plasmodium* species. Primaquine is added in the treatment of infections with *P vivax* and *P ovale* to eradicate the intrahepatic stages (hypnozoites) of these malarial species, which are responsible for relapses.

Pharmacology	Infectious Diseases	Malaria
Subject	System	Topic

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Pharmacology	Infectious Diseases	Malaria
Subject	System	Topic

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This patient has fever, chills, sweats, and red blood cell inclusions on Giemsa smear that developed following travel to a tropical geographic region

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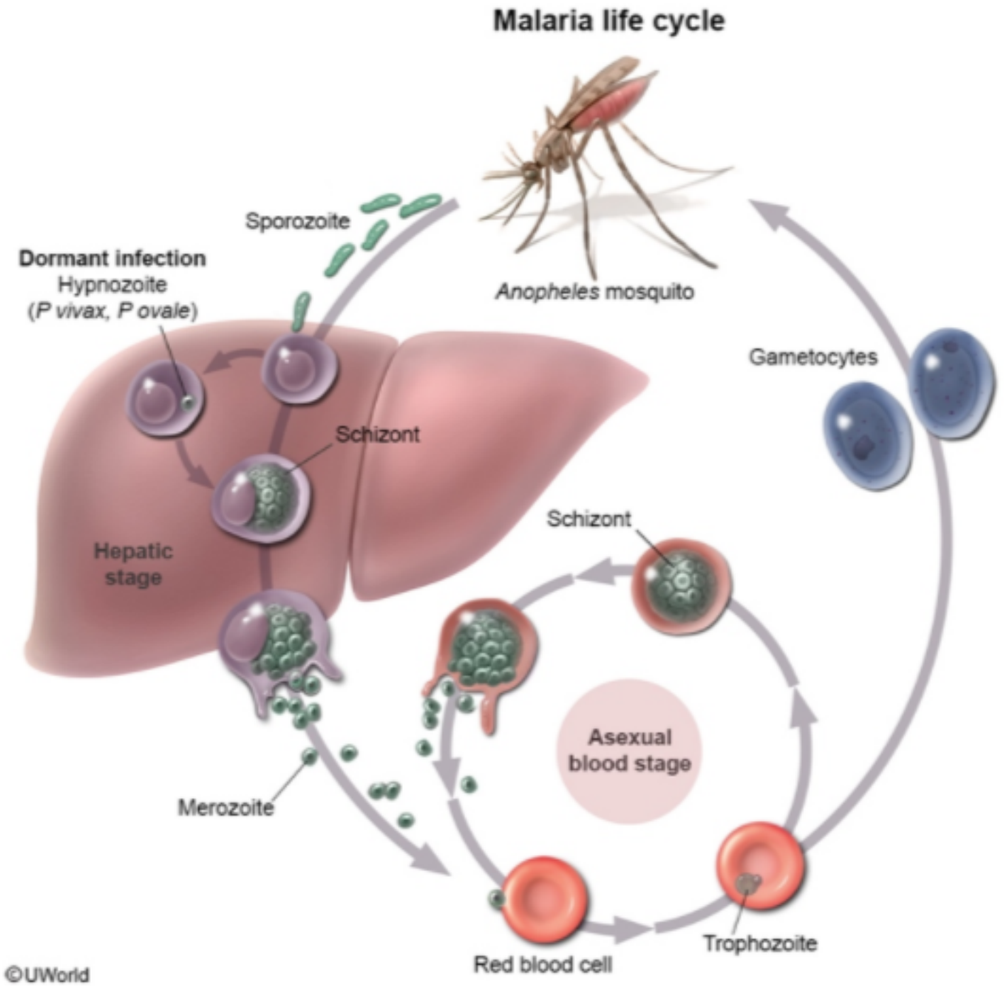

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A 64-year-old man comes to the office for follow-up after a recent hospitalization. Ten days ago, he was admitted due to fever, dysuria, urinary urgency, and perineal pain. Evaluation revealed acute prostatitis, and urine culture was positive for *Escherichia coli* that was sensitive to all tested antibiotics. He received intravenous ciprofloxacin with improvement in his symptoms and was subsequently discharged on oral ciprofloxacin. The patient has been taking the antibiotic as prescribed, but over the past 2 days he has had recurrent fever and dysuria. He takes diltiazem for palpitations, atorvastatin for hyperlipidemia, and an over-the-counter antacid for frequent heartburn. Temperature is 37.3 C (99.1 F), blood pressure is 118/68 mm Hg, and pulse is 90/min. Physical examination shows a mildly enlarged and tender prostate. Repeat urine culture grows *E coli*. Which of the following is the most likely cause of this patient's recurrent symptoms?

- A. Acquired antibiotic resistance
- B. Decreased drug bioavailability
- C. Exposure to untreated sexual partner
- D. Increased renal drug clearance
- E. Induction of hepatic CYP enzymes

Submit

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- A. Acquired antibiotic resistance (10%)
- ✓ B. Decreased drug bioavailability (57%)
- C. Exposure to untreated sexual partner (2%)
- D. Increased renal drug clearance (3%)
- E. Induction of hepatic CYP enzymes (25%)

Omitted
Correct answer
B

57%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

Chelation drug interactions	
	• Formation of insoluble compounds with polyvalent cations in the gastrointestinal

Chelation drug interactions	
Mechanism	• Formation of insoluble compounds with polyvalent cations in the gastrointestinal tract • Decreased absorption of drug
Commonly involved drugs	• Tetracyclines • Fluoroquinolones • Levothyroxine
Chelation cations	• Iron • Calcium • Magnesium • Aluminum

This patient has had a relapse of acute prostatitis despite an adequate initial response and good medication adherence. This treatment failure is likely due to a **drug-drug interaction** with his home medications.

Fluoroquinolones normally have very high bioavailability and near-complete absorption. However, they can form insoluble chelate complexes with **polyvalent cations** (eg, **calcium**, iron, aluminum, magnesium) in the gastrointestinal tract. This leads to **impaired absorption** and a significant decrease in drug bioavailability. In this patient's case, his initial response to the antibiotic reflects the parenteral dosing, which bypasses the gastrointestinal tract and avoids this potential interaction.

Over-the-counter **antacids** typically contain calcium, magnesium, and/or aluminum salts and are used by many patients for treatment of heartburn due to gastroesophageal reflux. Calcium salts (eg, calcium carbonate, calcium citrate) are also widely used in the treatment of osteoporosis. However, since these medications are available without a prescription and are often taken intermittently, the potential for interaction may not be apparent at the time antibiotic treatment is initiated.

(Choice A) Antimicrobial sensitivity testing of this patient's initial culture showed no significant fluoroquinolone resistance. In addition, he had a positive initial clinical response. Loss of effectiveness after changing to an oral formulation is more consistent with decreased bioavailability rather than antibiotic resistance.

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(Choice C) Prostatitis due to sexually transmitted organisms is typically seen with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and is more common with younger rather than older men. Reinfection with *E coli* via sexual contact is unlikely.

(Choice D) Ciprofloxacin is primarily cleared by renal excretion, and the dosage may need to be decreased in patients with significant renal impairment. However, switching this patient from parenteral to oral antibiotic therapy would not affect renal drug clearance.

(Choice E) Diltiazem is a cytochrome P450 (CYP3A4) inhibitor (not inducer) that can cause increased systemic levels of numerous drugs, leading to drug toxicity (eg, myopathy due to statins). Regardless, ciprofloxacin is primarily eliminated by renal excretion, and drug levels are unlikely to be significantly affected by P450 inducers.

Educational objective:
Fluoroquinolones can form insoluble chelate complexes with polyvalent cations (eg, calcium, iron, aluminum, magnesium) in the gastrointestinal tract, leading to impaired absorption. This effect can be seen with over-the-counter antacids containing calcium, magnesium, and/or aluminum salts and in patients taking calcium salts (eg, calcium carbonate, calcium citrate) for treatment of osteoporosis.

Pharmacology	Infectious Diseases	Quinolones
Subject	System	Topic

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A 77-year-old woman is brought to the emergency department due to fever and confusion. The patient has a history of Alzheimer dementia and lives in a nursing home. Temperature is 38.4 C (101.1 F), blood pressure is 104/74 mm Hg, pulse is 110/min, and respirations are 18/min. Suprapubic tenderness is present on physical examination. Urinalysis shows numerous bacteria and leukocytes, and urine culture grows *Pseudomonas aeruginosa*. Further analysis reveals that the isolated organism produces an enzyme that is located on the cytoplasmic surface of the cell membrane and that catalyzes the transfer of acetyl groups to exogenous substances. The bacteria are most likely resistant to which of the following antibiotics?

A. Ceftazidime
B. Ciprofloxacin
C. Gentamicin
D. Imipenem
E. Piperacillin

Submit

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- A. Ceftazidime (12%)
- B. Ciprofloxacin (13%)
- ✓ C. Gentamicin (40%)
- D. Imipenem (9%)
- E. Piperacillin (23%)

Omitted
Correct answer
C

40%
Answered correctly

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02/21/2020
Last Updated

Explanation

Common antibiotic resistance mechanisms	
Penicillins	• Beta-lactamase, ESBL • Mutated PBP

Common antibiotic resistance mechanisms	
Penicillins	• Beta-lactamase, ESBL • Mutated PBP • Mutated porin protein
Vancomycin	• Mutated peptidoglycan cell wall • Impaired influx/increased efflux
Quinolones	• Mutated DNA gyrase • Impaired influx/increased efflux
Aminoglycosides	• Aminoglycoside-modifying enzymes • Mutated ribosomal subunit protein • Mutated porin protein
Tetracyclines	• Impaired influx/increased efflux • Inactivated enzyme
Rifamycins	• Mutated RNA polymerase

ESBL = extended-spectrum beta-lactamase; PBP = penicillin-binding protein.

Pseudomonas aeruginosa is a gram-negative, opportunistic pathogen with multiple mechanisms of antibiotic resistance, including beta-lactamases, efflux pumps, and **antibiotic-modifying enzymes**. Antibiotic-modifying enzymes add chemical groups (eg, acetyl, adenyl, phosphate) to a target drug and are the most common mechanisms of **aminoglycoside** (eg, gentamicin) **resistance**. Altered aminoglycosides have a reduced ability to bind to the 16S ribosomal RNA within the 30S ribosomal subunit, leading to increased minimum inhibitory concentrations and reduced bactericidal effects. Most antibiotic-modifying enzymes arise via transfer of plasmids or transposons rather than chromosomal mutations.

(Choices A, D, and E) Cephalosporins (eg, ceftazidime), carbapenems (eg, imipenem), and penicillins (eg, piperacillin) are beta-lactam drugs

ESBL = extended-spectrum beta-lactamase; PBP = penicillin-binding protein.

Pseudomonas aeruginosa is a gram-negative, opportunistic pathogen with multiple mechanisms of antibiotic resistance, including beta-lactamases, efflux pumps, and **antibiotic-modifying enzymes**. Antibiotic-modifying enzymes add chemical groups (eg, acetyl, adenyl, phosphate) to a target drug and are the most common mechanisms of **aminoglycoside** (eg, gentamicin) **resistance**. Altered aminoglycosides have a reduced ability to bind to the 16S ribosomal RNA within the 30S ribosomal subunit, leading to increased minimum inhibitory concentrations and reduced bactericidal effects. Most antibiotic-modifying enzymes arise via transfer of plasmids or transposons rather than chromosomal mutations.

(Choices A, D, and E) Cephalosporins (eg, ceftazidime), carbapenems (eg, imipenem), and penicillins (eg, piperacillin) are beta-lactam drugs that exert their effect by interfering with the cell wall. Resistance to cephalosporins and penicillins occurs largely because of the bacterial secretion of beta-lactamase, an enzyme that hydrolyzes the beta-lactam ring and inactivates the antibiotic. Carbapenems are not very susceptible to most beta-lactamases due to additional chemical components surrounding their beta-lactam ring; however, resistance to carbapenems can occur due to carbapenemase, which is primarily seen in *Enterobacter* species.

(Choice B) Fluoroquinolones (eg, ciprofloxacin) block enzymes (DNA gyrase, topoisomerase) responsible for bacterial DNA synthesis. Resistance usually occurs due to genetic mutations that prevent drug binding to these enzymes or to the increased expression of antibiotic efflux pumps.

Educational objective:
Aminoglycoside (eg, gentamicin) resistance is most commonly due to antibiotic-modifying enzymes. These enzymes add chemical groups to the antibiotic, which diminishes its ability to bind to the 16S ribosomal RNA within the 30s ribosomal subunit.

References

- Mechanisms of antibiotic resistance.

Pharmacology	Infectious Diseases	Aminoglycoside
Subject	System	Topic

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A 24-year-old pregnant woman comes to the emergency department in active labor at full term. The patient has a history of HIV from injection drug use. She is not adherent with antiretroviral therapy and has had no recent testing of CD4 count or plasma viral load. Physical examination shows regular uterine contractions, ruptured amniotic membranes, and a fully dilated cervix. A decision is made to continue with the vaginal delivery due to advanced labor. Intravenous zidovudine is administered to the patient during the delivery and to the infant immediately after birth. This medication helps decrease the risk of perinatal transmission by inhibiting which of the following components of viral genome replication?

A. Folate-dependent uracil methylation

B. Integration of viral DNA into the host genome

C. Nucleoside phosphorylation

D. Phosphodiester bond formation

E. Proper base pairing and hydrogen bond formation

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A. Folate-dependent uracil methylation (1%)
B. Integration of viral DNA into the host genome (21%)
C. Nucleoside phosphorylation (21%)
✓ D. Phosphodiester bond formation (34%)
E. Proper base pairing and hydrogen bond formation (21%)

Omitted
Correct answer
D

34%
Answered correctly

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Time Spent

05/25/2020
Last Updated

Explanation

HIV is a single-stranded RNA virus that is converted into cDNA by the HIV enzyme **reverse transcriptase**. This enzyme grows DNA by adding nucleotides to the terminal 3′-hydroxyl group using a 3′-5′ **phosphodiester bond**. **Nucleoside reverse transcriptase inhibitors** (NRTIs) such as zidovudine block this step in viral replication. This class of medications is composed of nucleoside/nucleotide analogues that **do not have a 3′-hydroxyl group**. When reverse transcriptase incorporates an NRTI into a growing DNA strand, it results in chain termination because no 3′-hydroxyl group is available to add additional base pairs.

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Zidovudine (ZDT) was the first approved HIV medication but is now used primarily to prevent maternal to fetal transmission of HIV during labor and delivery. It is a thymidine analogue that contains an azido group in place of the hydroxyl group usually found at the 3′ end of thymidine.

(Choice A) The enzyme thymidylate synthase catalyzes the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). N5, N10-methylene tetrahydrofolate is the methyl donor in this reaction and is converted to dihydrofolate (DHF) in the process. Tetrahydrofolate is then regenerated from DHF by dihydrofolate reductase. Methotrexate is a chemotherapeutic agent that inhibits DNA synthesis by inhibiting dihydrofolate reductase.

(Choice B) Integration of viral DNA into the host genome is mediated by integrase, an HIV enzyme that is inhibited by integrase strand transfer inhibitors (eg, raltegravir).

(Choice C) Inhibition of nucleoside phosphorylation is not an effect of ZDT. In fact, nucleoside reverse transcriptase inhibitors (including ZDT) must be phosphorylated within the host cell to form the functional triphosphate moiety. Non-nucleoside reverse transcriptase inhibitors can bind directly to (and inactivate) reverse transcriptase without being phosphorylated.

(Choice E) In double-stranded DNA, A always pairs with T, and G always pairs with C. These bases bind via hydrogen bonds. Some chemotherapeutic agents, such as the anthracyclines daunorubicin and doxorubicin, intercalate between the bases, causing defective base pairing and splitting of the DNA strands. Transcription and replication failure and mutagenesis ultimately result.

Educational objective:
Zidovudine (ZDT) is a nucleoside reverse transcriptase inhibitor used to prevent maternal to fetal transmission of HIV during labor (when the mother is not virally suppressed). It is a thymidine analogue that does not have the normal 3′-hydroxyl group found on thymidine. Because new nucleotides are added to growing DNA chains only at the 3′-hydroxyl group, the addition of ZDT into DNA results in chain termination.

Pharmacology Infectious Diseases Antiretroviral therapy

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A 45-year-old woman with advanced HIV infection has been receiving antiretroviral therapy for several years. When treatment was first initiated, the patient's viral load rapidly decreased to undetectable levels and her CD4+ cell count remained above 200/mm^3. However, recent HIV RNA levels have increased above the detection threshold. After undergoing drug resistance testing, she is started on an integrase inhibitor, and her viral load decreases precipitously. Which of the following steps of viral replication is most likely to be inhibited as a result of this patient's new treatment?

A. Cleavage of a viral polyprotein precursor

B. Complementary DNA synthesis from a viral RNA template

C. Fusion of viral and host phospholipid bilayers

D. Production of viral messenger RNA

E. Viral attachment to host cells

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- A. Cleavage of a viral polyprotein precursor (18%)
- B. Complementary DNA synthesis from a viral RNA template (24%)
- C. Fusion of viral and host phospholipid bilayers (12%)
- ✓ D. Production of viral messenger RNA (35%)
- E. Viral attachment to host cells (7%)

Omitted
Correct answer
D

35%
Answered correctly

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02/08/2020
Last Updated

Explanation

HIV antiviral drugs

HIV virion

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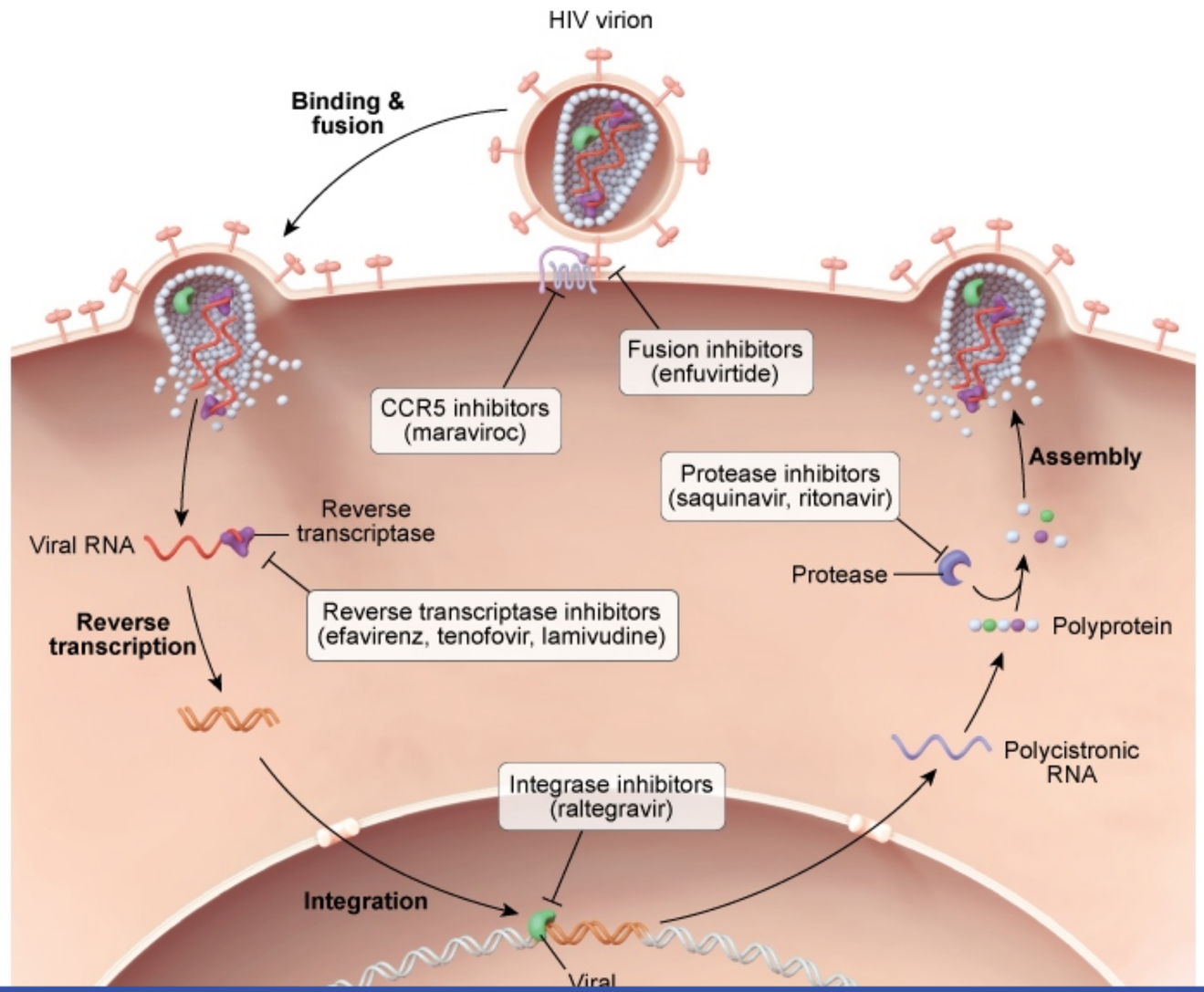
HIV antiviral drugs



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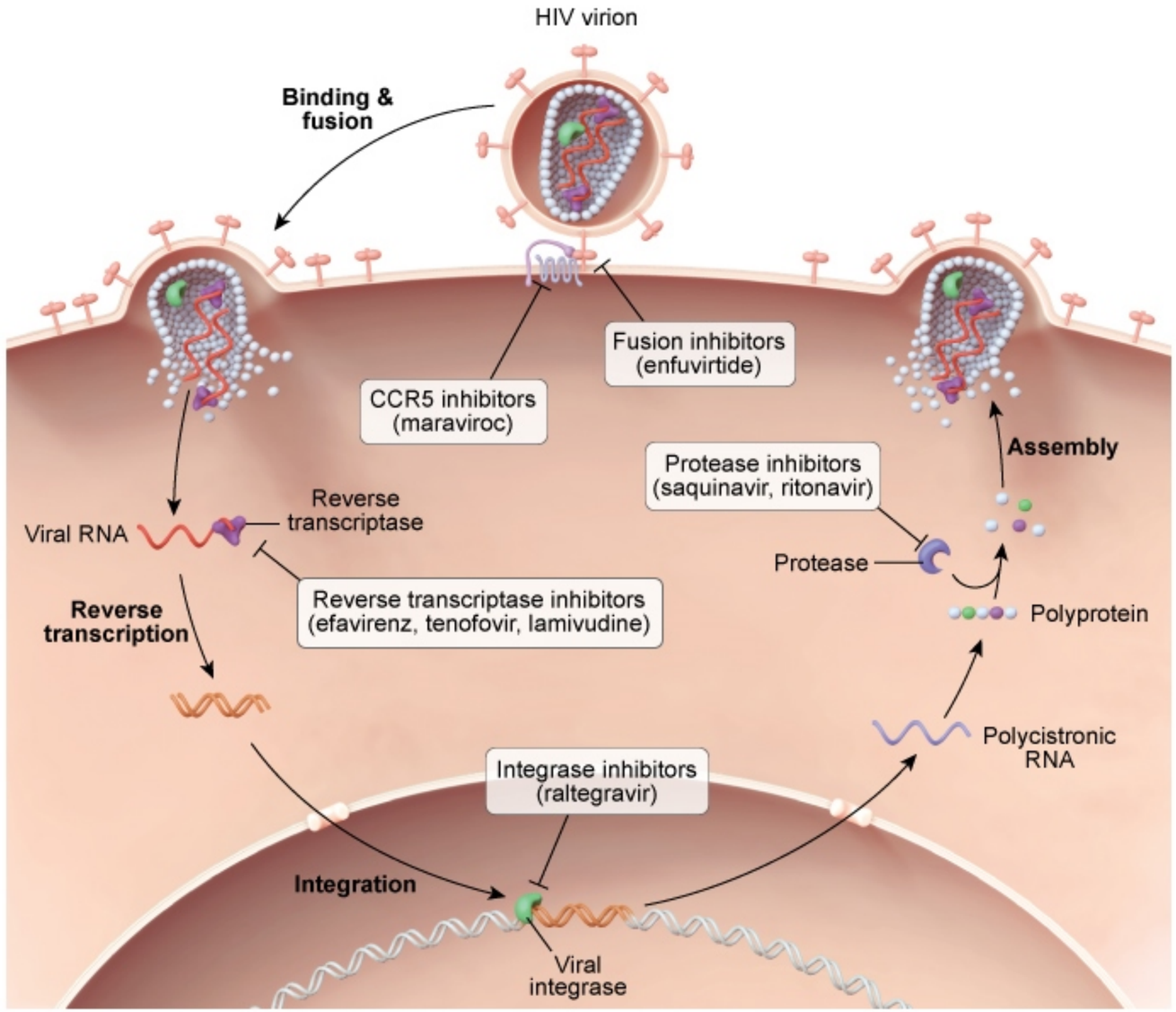
HIV antiviral drugs



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After an HIV virion enters a host cell, viral RNA is released from the nucleocapsid and transcribed into **double-stranded DNA** by reverse transcriptase. The viral DNA then enters the nucleus and, through the actions of **integrase**, permanently **inserts into** the host cell's **chromosomes** to become a provirus. RNA polymerase II then transcribes viral mRNA from the proviral DNA. Once synthesized, HIV mRNA exits through the nuclear pores into the cytoplasm, where it uses the host cell's ribosomes to translate the enzymes, glycoproteins, structural proteins, and regulatory proteins needed to promote viral replication and transmission. The full-length mRNA also serves as the viral genome that is packaged into newly synthesized virions.

Raltegravir is an **integrase inhibitor** that disrupts the ability of double-stranded HIV DNA to integrate into the host cell's chromosomes. In the absence of integration, the **viral genome cannot be transcribed** by host cellular machinery and is eventually degraded by nucleases.

(Choice A) Most of the proteins necessary for HIV replication are translated into a polyprotein precursor that is then cleaved into individual proteins by viral and cellular protease enzymes. The action of viral protease can be directly prevented by protease inhibitors such as saquinavir.

(Choice B) Complementary DNA synthesis from the HIV RNA template is directly impaired by nucleoside and non-nucleoside reverse transcriptase inhibitors.

(Choice C) Drugs that bind to gp41, HIV's transmembrane envelope protein, are known as fusion inhibitors (eg, enfuvirtide). These drugs prevent gp41 from undergoing the conformational changes necessary for viral membrane fusion with the host cell membrane.

(Choice E) For HIV to infect a cell, the envelope glycoprotein gp120 must bind to both a CD4 molecule and a chemokine receptor (eg, CXCR4 or CCR5). CCR5 antagonists, such as maraviroc, exert their antiviral activity against HIV by blocking attachment and entry of CCR5-tropic viruses into CD4+ T cells and macrophages.

Educational objective:
Integration of double-stranded HIV DNA into the host cell's chromosomes is necessary to induce viral gene expression and prevent degradation of the viral genome. Raltegravir is an integrase inhibitor that disrupts HIV genome integration, preventing synthesis of viral mRNA.

References

- Raltegravir: the first HIV-1 integrase strand transfer inhibitor in the HIV armamentarium.

Pharmacology Infectious Diseases Antiretroviral therapy

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A 5-year-old girl is brought to the physician by her parents because of intense perianal itching, especially during the night. The child is otherwise healthy and her development has been normal. Physical examination shows perianal excoriation. Cellulose adhesive tape is applied to the perianal area of the child shortly after she wakes up in the morning. Microscopic analysis of the tape reveals the presence of eggs that are asymmetrically flattened on one side. Which of the following is the most appropriate treatment for this patient's condition?

A. Albendazole
B. Diethylcarbamazine
C. Ivermectin
D. Nifurtimox
E. Praziquantel

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- ✓ A. Albendazole (79%)
- B. Diethylcarbamazine (1%)
- C. Ivermectin (8%)
- D. Nifurtimox (1%)
- E. Praziquantel (9%)

Omitted
Correct answer
A

79%
Answered correctly

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Time Spent

02/03/2020
Last Updated

Explanation

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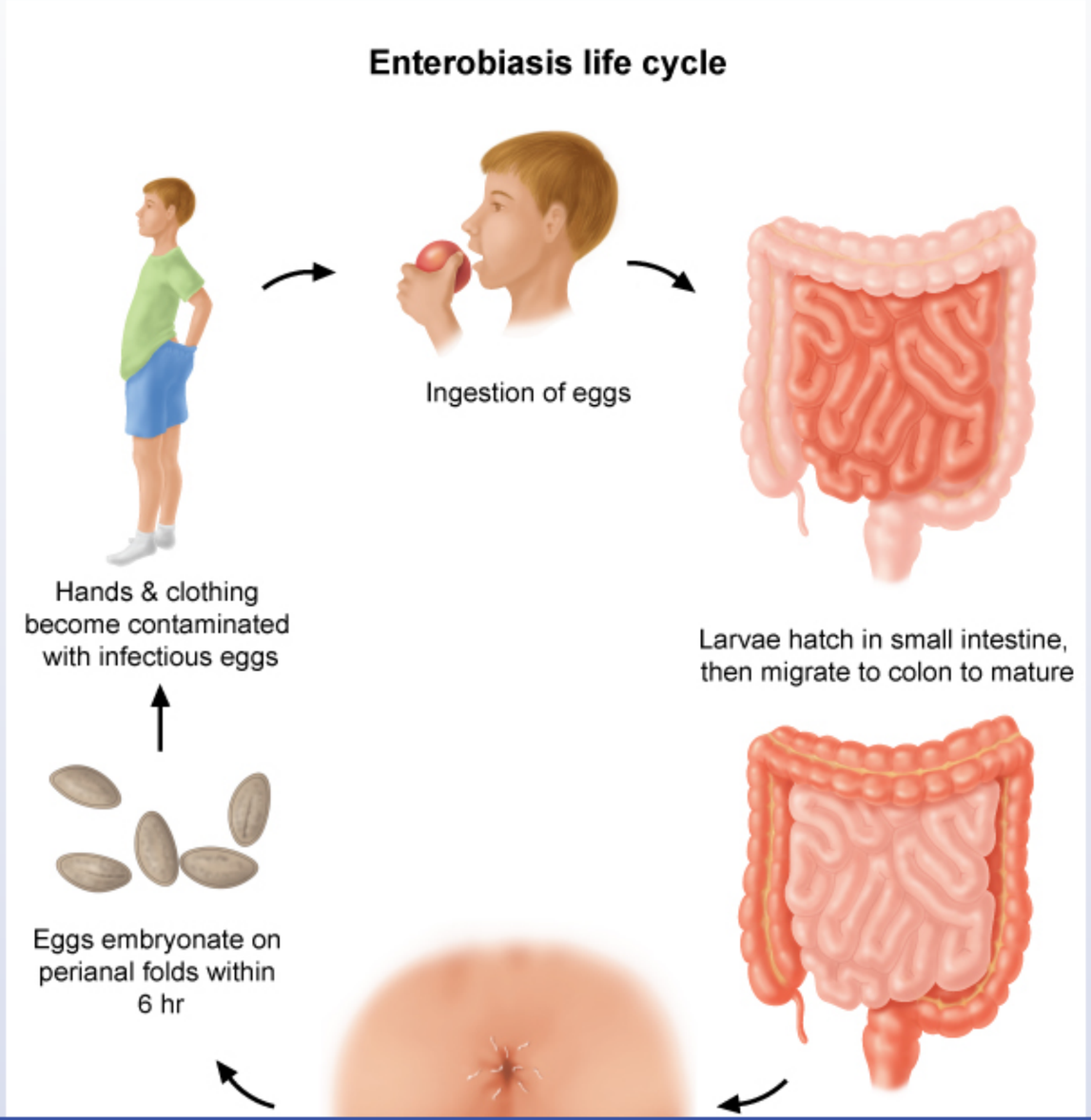

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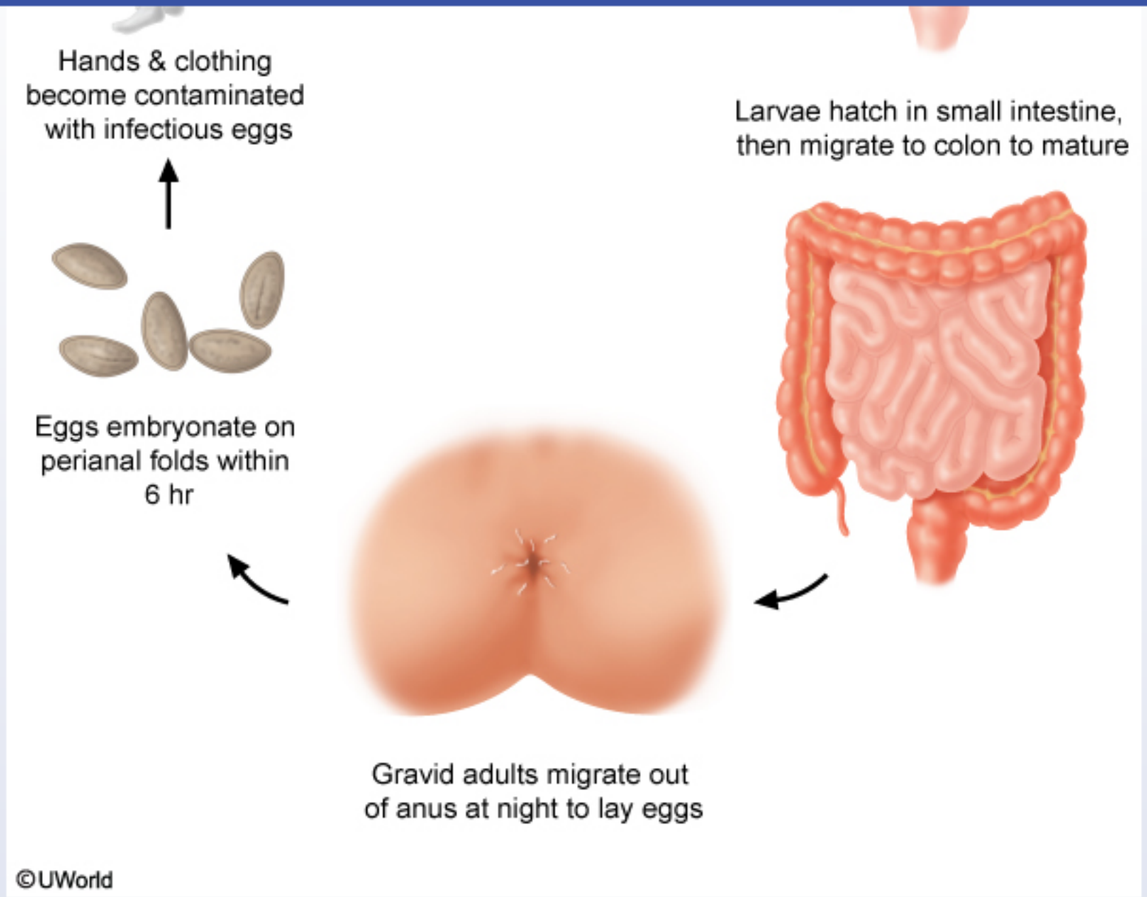

Enterobiasis is the most common helminthic infection in the United States, occurring most frequently in **children** age 5-10. The etiologic organism is the **pinworm** (*Enterobius vermicularis*). It has a simple life cycle, which contributes to its high prevalence. The adult worms live in the human intestine, particularly in the cecum and appendix. In contrast to other worms that release their eggs into the intestine, the female worm migrates out through the rectum onto the perianal skin to deposit eggs (most commonly at night). Larvae inside the eggs mature within 6 hours and can either be ingested by the same individual (autoinfection) or spread to other humans.

The presence of eggs and worms in the perianal area causes an inflammatory reaction resulting in **perianal itching**, also known as pruritus ani. Abdominal pain, nausea, and vomiting can also manifest in patients with a heavy worm burden. Diagnosis is made by the **Scotch tape test** (ie

of anus at night to lay eggs

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The presence of eggs and worms in the perianal area causes an inflammatory reaction resulting in **perianal itching**, also known as pruritus ani. Abdominal pain, nausea, and vomiting can also manifest in patients with a heavy worm burden. Diagnosis is made by the **Scotch tape test** (ie, microscopy of adhesive tape applied to perianal region), which reveals the presence of oval, asymmetrically flattened eggs with a bean-shaped appearance. **Albendazole** is the first-line treatment; **pyrantel pamoate** is an alternate agent preferred in pregnant patients.

(Choice B) Diethylcarbamazine is indicated for the treatment of *Loa loa* (loiasis) and *Wuchereria bancrofti* (lymphatic filariasis) infections.

(Choice C) Ivermectin is used to treat infections caused by *Strongyloides stercoralis* (strongyloidiasis) and *Onchocerca volvulus* (onchocerciasis).

(Choice D) Nifurtimox is used to treat diseases caused by trypanosomes, including Chagas disease (*Trypanosoma cruzi*).

(Choice E) Infections caused by *Schistosoma* (schistosomiasis), *Clonorchis sinensis* (clonorchiasis), and *Paragonimus westermani* (paragonimiasis) are treated with praziquantel.

Educational objective:
Enterobius vermicularis infection (enterobiasis) occurs most frequently in school-age children and presents with perianal pruritus. Diagnosis is made by the Scotch tape test. Albendazole is the first-line treatment, with pyrantel pamoate as an alternate agent preferred in pregnant patients.

Pharmacology	Infectious Diseases	Intestinal helminth parasites
Subject	System	Topic

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A 28-year-old woman comes to the office due to several months of progressive abdominal pain and intermittent diarrhea. She denies fever or chills but has lost weight due to poor appetite. The patient works for an organization that installs wood pellet cookstoves in rural villages in Central Africa and has spent much time in the region over the last 5 years. Temperature is 37.8 C (100 F), blood pressure is 126/72, and pulse is 86. BMI is 19 kg/m^2. Physical examination is normal. Laboratory results are as follows:

Complete blood count

Hemoglobin	9.5 g/dL
Platelets	195,000/mm^3
Leukocytes	8,800/mm^3
Neutrophils	54%
Eosinophils	14%
Lymphocytes	32%

An intestinal biopsy sample is shown in the exhibit. Which of the following is the most appropriate treatment for this patient?

A. Artemisinin-based combination therapy
B. Ciprofloxacin
C. Ganciclovir
D. Metronidazole plus paromomycin
E. Praziquantel

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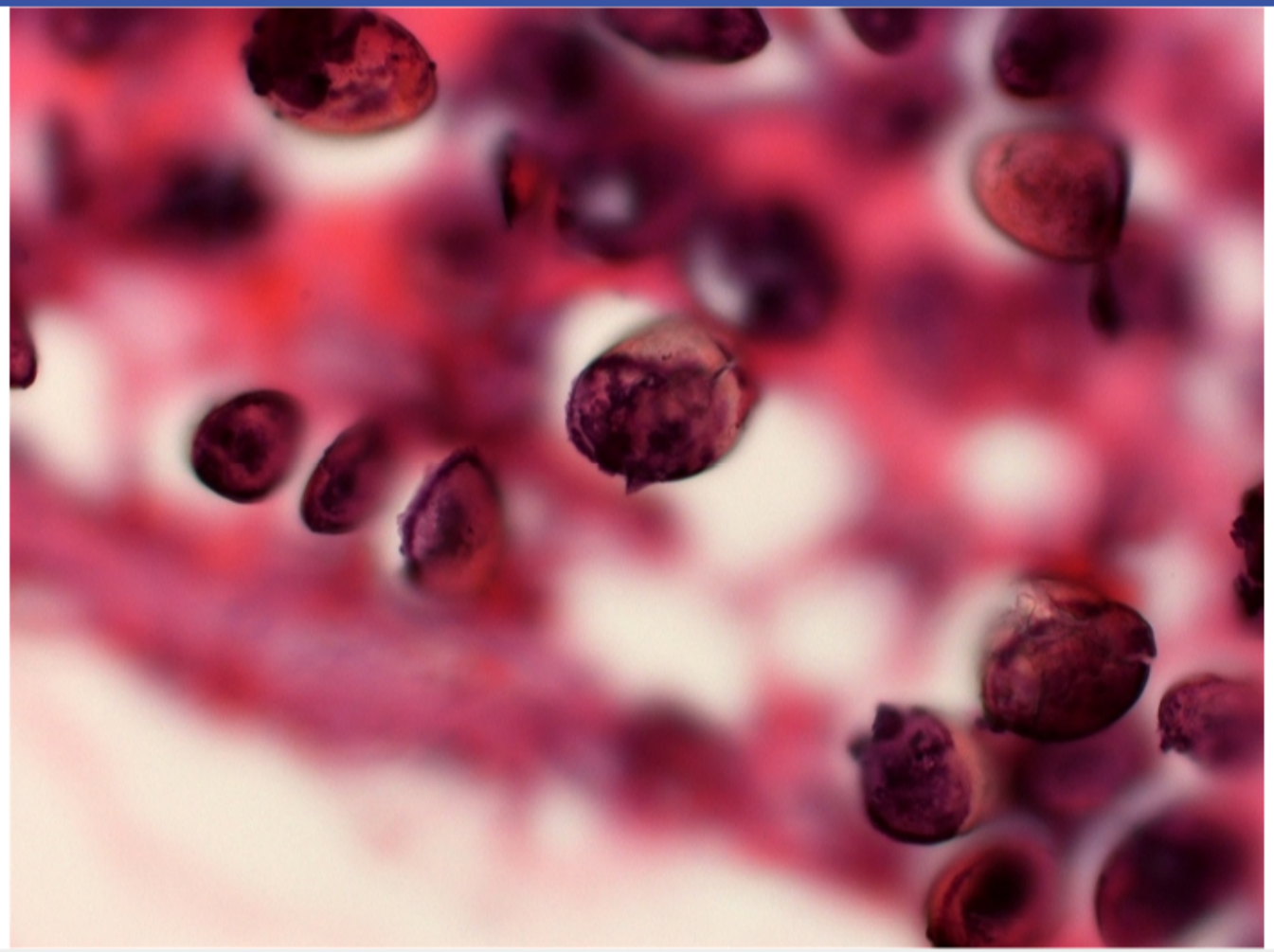

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Leukocytes	8,800/mm^3
Neutrophils	54%
Eosinophils	14%
Lymphocytes	32%

An intestinal biopsy sample is shown in the exhibit. Which of the following is the most appropriate treatment for this patient?

A. Artemisinin-based combination therapy (6%)
B. Ciprofloxacin (1%)
C. Ganciclovir (0%)
D. Metronidazole plus paromomycin (39%)
✓ E. Praziquantel (51%)

Omitted

Schistosomiasis		
***Schistosoma* species**	**Location**	**Symptoms**
S haematobium	• North Africa • Sub-Saharan Africa • Middle East	**Urinary schistosomiasis** • Terminal hematuria, dysuria & frequent urination • Hydronephrosis, pyelonephritis & squamous cell carcinoma of the bladder
S mansoni	• Sub-Saharan Africa • Middle East • South America • Caribbean	**Intestinal schistosomiasis** • Diarrhea & abdominal pain • Intestinal ulceration → iron deficiency anemia **Hepatic schistosomiasis** • Hepatomegaly, splenomegaly • Periportal fibrosis & subsequent portal hypertension
S japonicum	• Asia, particularly China • Philippines • Japan	

This patient's travel history, chronic intestinal symptoms, eosinophilia, and biopsy findings suggest **schistosomiasis**, a parasitic blood fluke infection primarily seen in rural parts of **sub-Saharan Africa** and East Asia. Exposure occurs when humans swim or bath in freshwater that contains **contaminated snails** (the intermediate host). Cercariae from the snails penetrate human skin and migrate to the **liver**, where they mature into adult worms. Adult worms then travel through the portal circulation to the **mesenteric** venules (*S mansoni* and *S japonicum*) or the venous plexus of the **bladder** (*S haematobium*).

Adult worms release eggs through host tissue to be excreted in feces or urine. Although most patients are asymptomatic, eggs can trigger a significant **granulomatous inflammatory response**, leading to manifestations in the **gastrointestinal tract** (eg, diarrhea, weight loss, anorexia, anemia), bladder (eg, terminal hematuria), or periportal system (eg, portal hypertension, splenomegaly). **Eosinophilia** is common early in the disease course as eosinophils release granules that are toxic to adult worms.

Diagnostic confirmation requires the identification of **round/oval eggs** with a characteristic terminal (*S. haematobium*) or lateral spine (*S. mansoni*) on stool/urinary testing or tissue biopsy. Treatment with **praziquantel**, which alters parasite digestion and calcium transport, is generally

mature into adult worms. Adult worms then travel through the portal circulation to the **mesenteric** venules (*S mansoni* and *S japonicum*) or the venous plexus of the **bladder** (*S haematobium*).

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(Choice A) Artemisinin-based combination therapy is used for chloroquine resistant malaria. Malaria can cause gastrointestinal symptoms, but patients are usually acutely ill (eg, fever, chills, myalgia headache). Giemsa-stained blood smear generally reveals intraerythrocytic ring-shaped trophozoites, not eggs with a spine.

(Choice B) Bacterial infection of the gastrointestinal tract is common when traveling to countries with poor sanitation and water control systems. Ciprofloxacin is sometimes used for treatment. However, most cases are brief in duration, eosinophilia is not generally seen, and eggs would not be present.

(Choice C) Ganciclovir can treat cytomegalovirus colitis, which frequently causes diarrhea and abdominal pain. However, most cases arise in patients that are severely immunocompromised. Furthermore, fever is usually present and biopsy would show intracytoplasmic and intranuclear inclusions, not eggs.

(Choice D) Metronidazole plus paromomycin is used to treat *Entamoeba histolytica*, which is a common cause of dysentery (eg, diarrhea, fever, abdominal pain) in travelers. However, the presence of several months of symptoms, eosinophilia, and eggs on biopsy make this diagnosis unlikely.

Educational objective:
Schistosomiasis is a blood fluke infection that occurs when humans bathe or swim in freshwater that contains contaminated snails. Adult worms mature in the liver, lodge in the mesenteric venules or vesicular venous plexus, and secrete eggs into feces or urine. Eggs can trigger granulomatous inflammation, leading to symptoms in the gastrointestinal, urinary, or periportal tract. Diagnosis is typically made when round or

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(Choice B) Bacterial infection of the gastrointestinal tract is common when traveling to countries with poor sanitation and water control systems. Ciprofloxacin is sometimes used for treatment. However, most cases are brief in duration, eosinophilia is not generally seen, and eggs would not be present.

(Choice C) Ganciclovir can treat cytomegalovirus colitis, which frequently causes diarrhea and abdominal pain. However, most cases arise in patients that are severely immunocompromised. Furthermore, fever is usually present and biopsy would show intracytoplasmic and intranuclear inclusions, not eggs.

(Choice D) Metronidazole plus paromomycin is used to treat *Entamoeba histolytica*, which is a common cause of dysentery (eg, diarrhea, fever, abdominal pain) in travelers. However, the presence of several months of symptoms, eosinophilia, and eggs on biopsy make this diagnosis unlikely.

Educational objective:
Schistosomiasis is a blood fluke infection that occurs when humans bathe or swim in freshwater that contains contaminated snails. Adult worms mature in the liver, lodge in the mesenteric venules or vesicular venous plexus, and secrete eggs into feces or urine. Eggs can trigger granulomatous inflammation, leading to symptoms in the gastrointestinal, urinary, or periportal tract. Diagnosis is typically made when round or oval eggs with a terminal or lateral spine are identified in urine, feces, or biopsy.

Pharmacology	Infectious Diseases	Schistosomiasis
Subject	System	Topic

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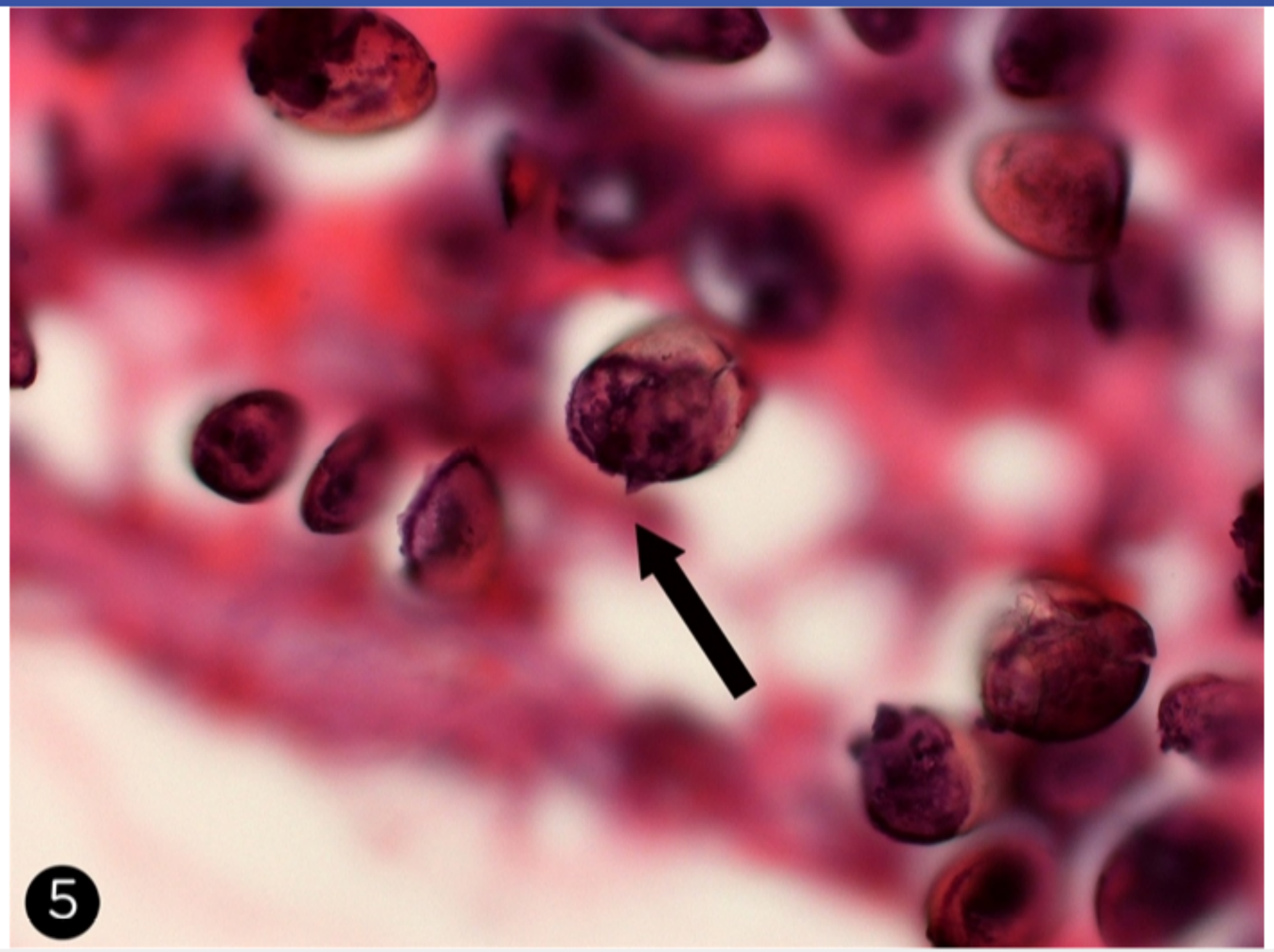

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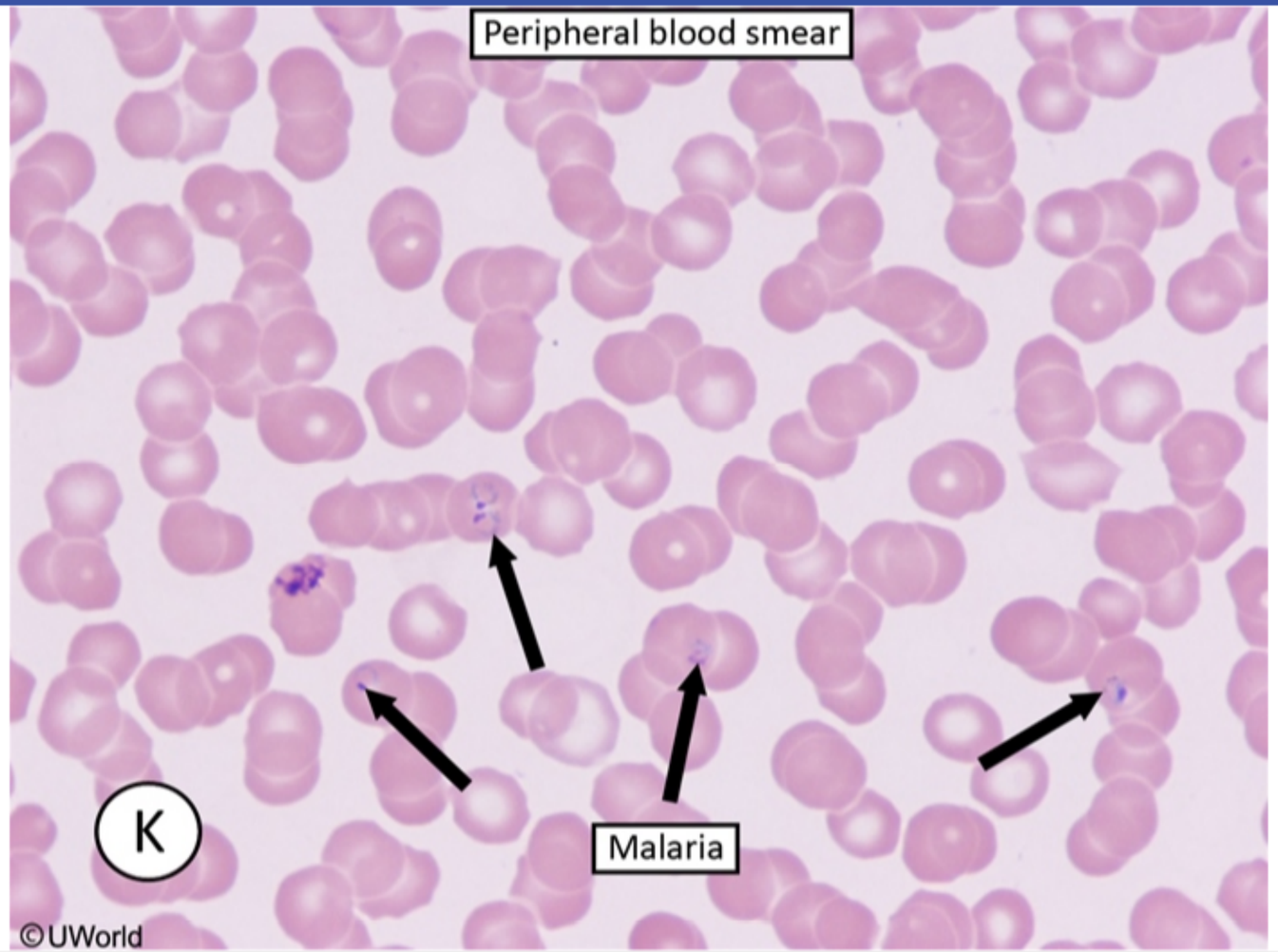

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infection primarily seen in rural parts of **sub-Saharan Africa** and East Asia. Exposure occurs when humans swim or bath in freshwater that contains **contaminated snails** (the intermediate host). Cercariae from the snails pe mature into adult worms. Adult worms then travel through the portal circulation to th venous plexus of the **bladder** (*S haematobium*).

Adult worms release eggs through host tissue to be excreted in feces or urine. Altho significant **granulomatous inflammatory response**, leading to manifestations in th anemia), bladder (eg, terminal hematuria), or periportal system (eg, portal hypertens disease course as eosinophils release granules that are toxic to adult worms.

Diagnostic confirmation requires the identification of **round/oval eggs** with a charac *mansoni*) on stool/urinary testing or tissue biopsy. Treatment with **praziquantel**, wh curative.

(Choice A) Artemisinin-based combination therapy is used for chloroquine resistant patients are usually acutely ill (eg, fever, chills, myalgia headache). Giemsa-stained trophozoites, not eggs with a spine.

(Choice B) Bacterial infection of the gastrointestinal tract is common when traveling Ciprofloxacin is sometimes used for treatment. However, most cases are brief in du be present.

(Choice C) Ganciclovir can treat cytomegalovirus colitis, which frequently causes d patients that are severely immunocompromised. Furthermore, fever is usually prese inclusions, not eggs.

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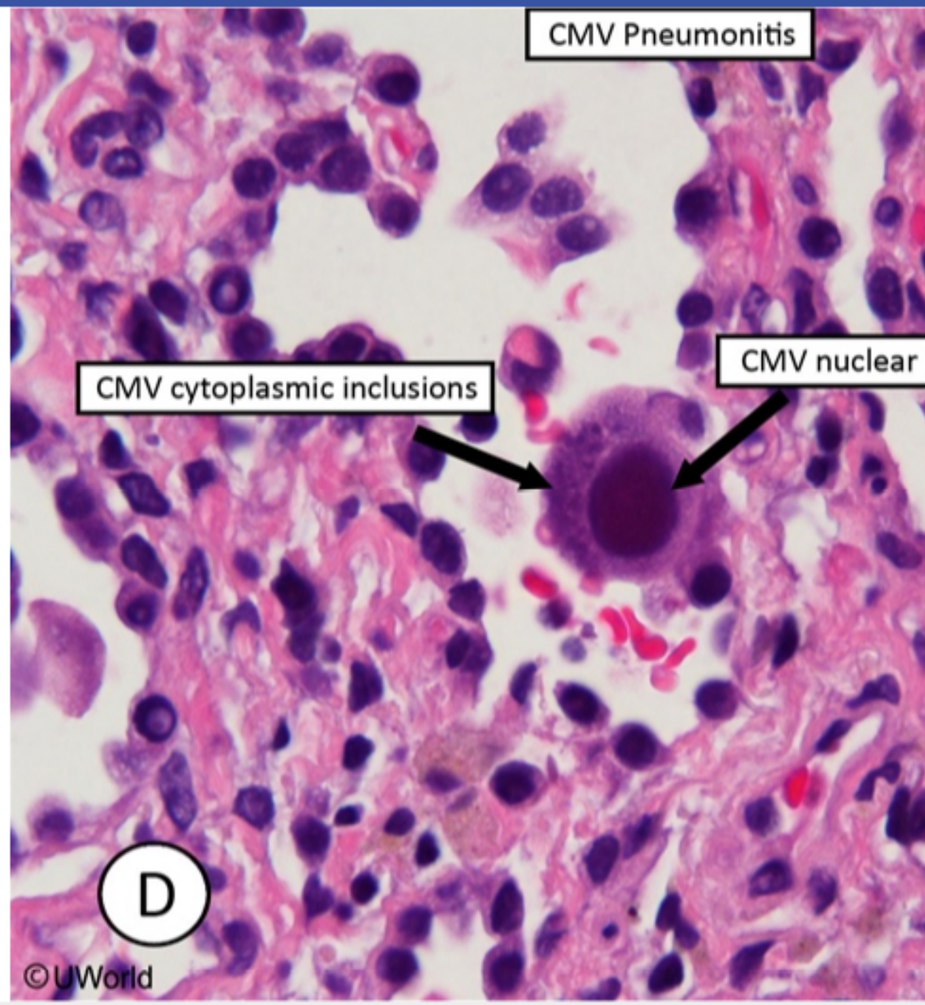
(C *ba histolytica* abdominal pain) in travelers. However, the presence of several months of symptom unlikely.

Educational objective:
Schistosomiasis is a blood fluke infection that occurs when humans bathe or swim in freshwater that contains contaminated snails. Adult worms

Exhibit Display



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A 28-year-old man comes to the office due to a rash. He has a history of seizure disorder and has been taking phenytoin for 6 years. Examination shows a diffuse, macular rash and lymphadenopathy. Biopsy of a lymph node is shown in the exhibit. Treatment of this patient's condition is most likely to involve which of the following?

A. Blockade of viral reverse transcriptase and integrase

B. Diminished type IV delayed hypersensitivity reaction

C. Inhibition of bacterial DNA gyrase and topoisomerase

D. Inhibition of transpeptidase and bacterial cell wall cross-linking

E. Reduced production of dihydrofolic acid and tetrahydrofolic acid

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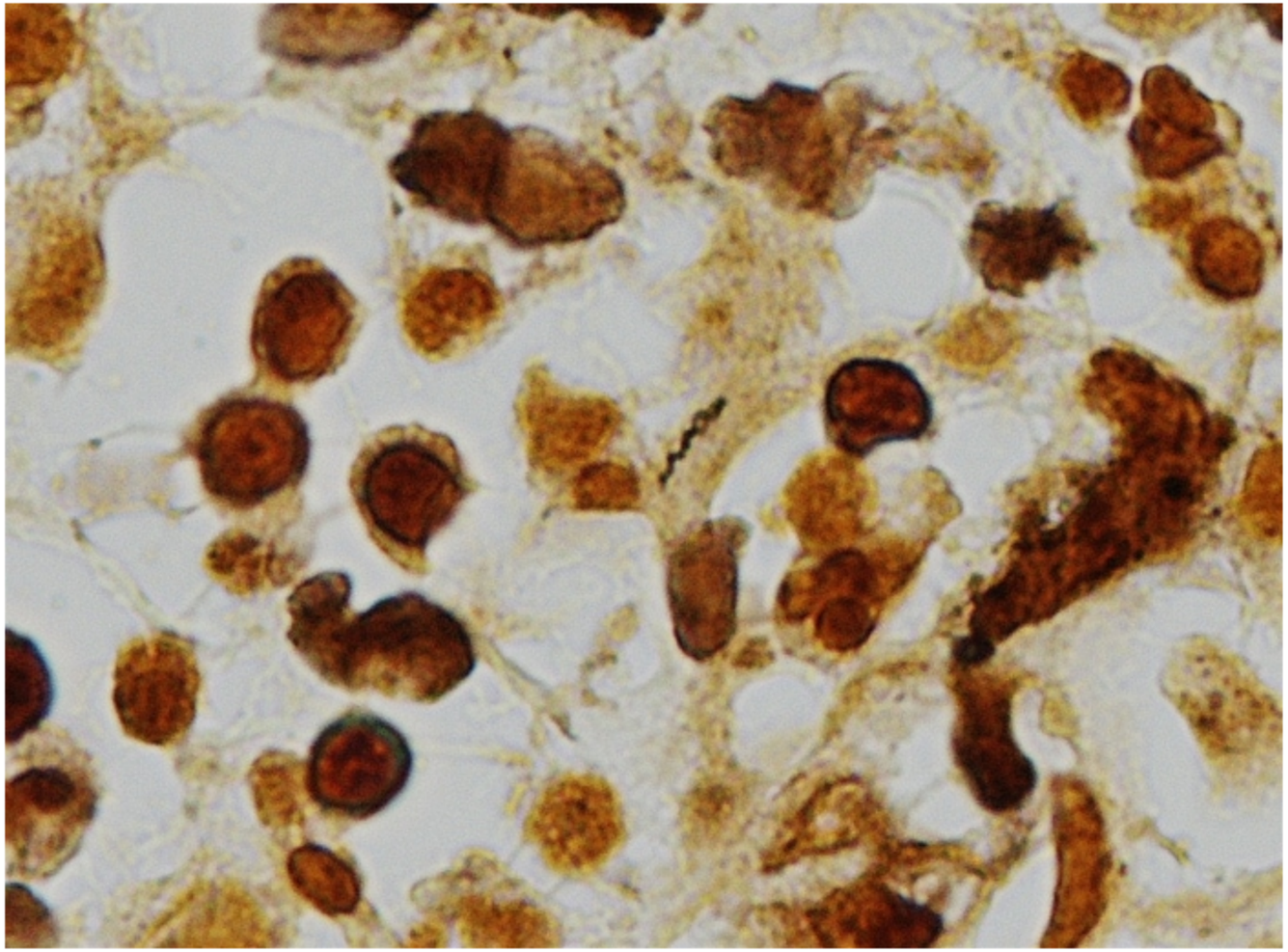

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A 28-year-old man comes to the office due to a rash. He has a history of seizure disorder and has been taking phenytoin for 6 years. Examination shows a diffuse, macular rash and lymphadenopathy. Biopsy of a lymph node is shown in the exhibit. Treatment of this patient's condition is most likely to involve which of the following?

A. Blockade of viral reverse transcriptase and integrase (8%)

B. Diminished type IV delayed hypersensitivity reaction (23%)

C. Inhibition of bacterial DNA gyrase and topoisomerase (10%)

✓ D. Inhibition of transpeptidase and bacterial cell wall cross-linking (35%)

E. Reduced production of dihydrofolic acid and tetrahydrofolic acid (21%)

Omitted
Correct answer
D

35%
Answered correctly

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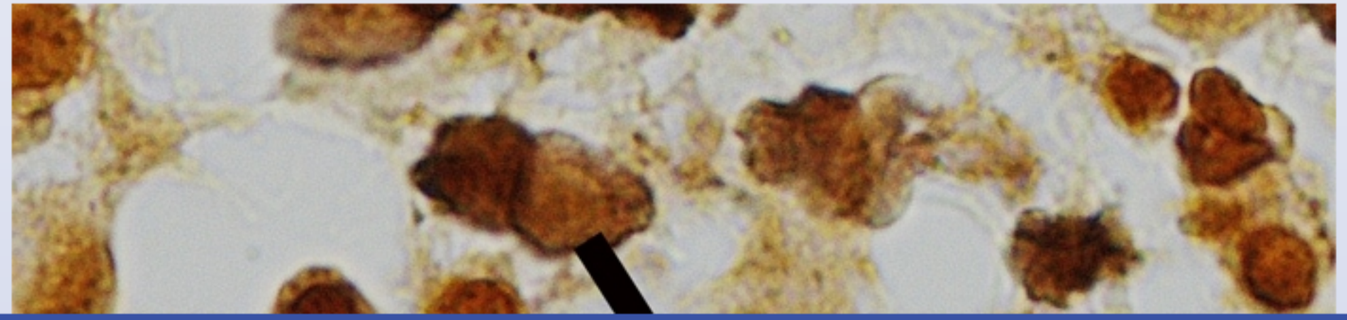
03/09/2020
Last Updated

Explanation



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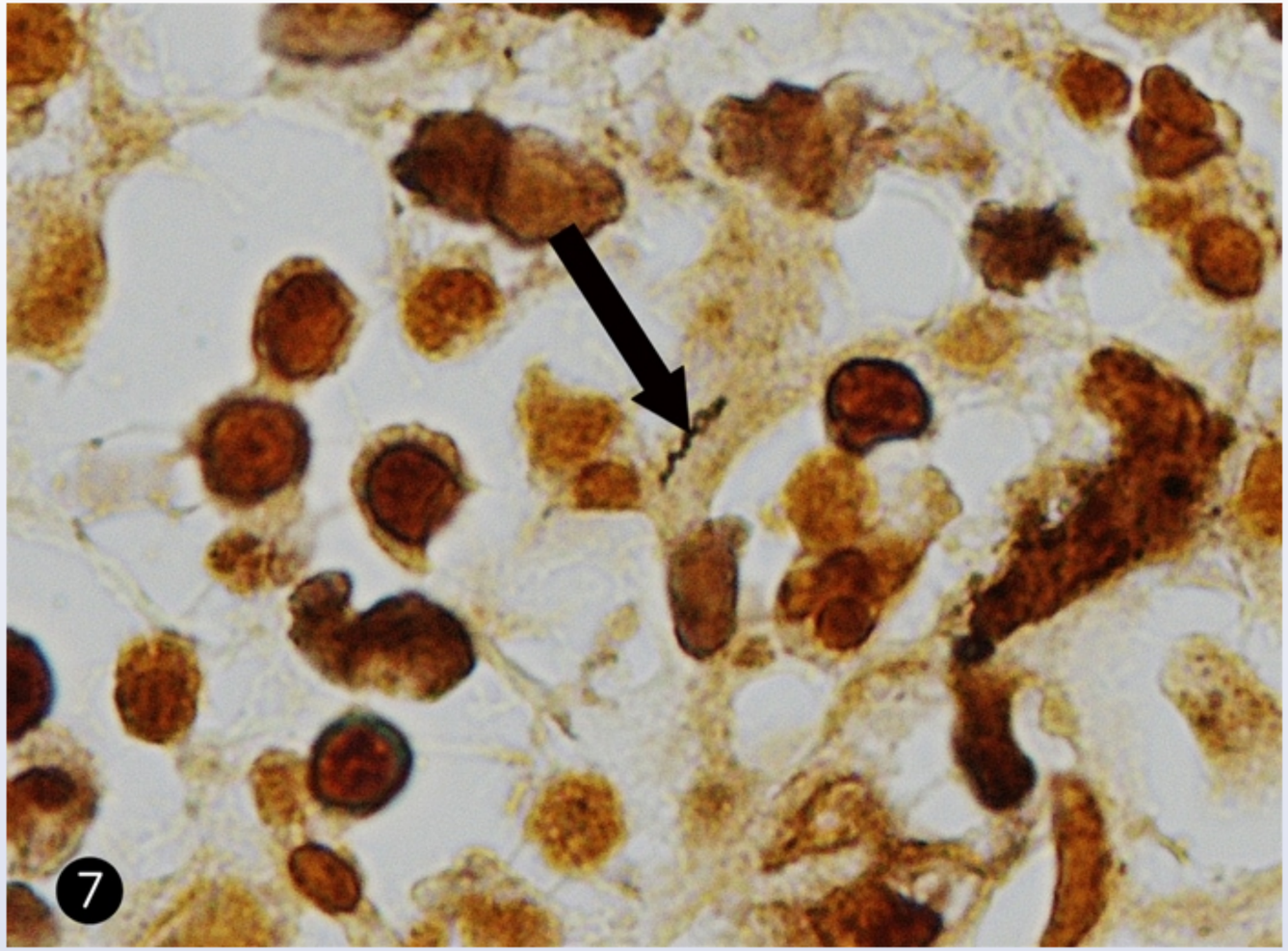


The presence of a generalized rash, lymphadenopathy, and a **corkscrew-shaped organism** on histopathology suggests **secondary syphilis**, a spirochetal infection caused by *Treponema pallidum*. Inoculation occurs via skin-to-skin contact during sexual intercourse; replication of *T pallidum* at the site of transmission results in an ulcer with heaped up borders (primary syphilis). Subsequent spread through the dermal lymphatic

The presence of a generalized rash, lymphadenopathy, and a **corkscrew-shaped organism** on histopathology suggests **secondary syphilis**, a spirochetal infection caused by *Treponema pallidum*. Inoculation occurs via skin-to-skin contact during sexual intercourse; replication of *T pallidum* at the site of transmission results in an ulcer with heaped up borders (primary syphilis). Subsequent spread through the dermal lymphatic system leads to systemic spread.

Secondary syphilis develops in untreated patients weeks or months after the chancre has resolved. Common manifestations include a **diffuse, macular rash** and **generalized lymphadenopathy**. The diagnosis is generally made with nontreponemal (eg, rapid plasma reagin) and treponemal-specific (eg, fluorescent treponemal antibody absorption) serologic testing because microscopy is technically difficult and less sensitive. However, **dark-field microscopy** or specialized silver stains (above image) can identify the spirochete.

All stages of syphilis are most effectively treated with **penicillin**, a beta-lactam antibiotic that disrupts cell wall synthesis by **inhibiting** transpeptidase, a bacterial enzyme necessary for **cell wall cross-linking**. Because penicillin is effective only against bacteria that are dividing, and because *T pallidum* replicates slowly, penicillin preparations that provide prolonged exposure (eg, intramuscular penicillin G benzathine) are required.

(Choice A) HIV is typically treated with reverse transcriptase and integrase inhibitors. Although acute HIV infection often presents with rash, lymphadenopathy, and constitutional symptoms a few weeks after transmission, a spiral-shaped organism would not be seen on biopsy.

(Choice B) Phenytoin can cause a diffuse rash due to a delayed type IV hypersensitivity reaction. However, most cases arise within a few weeks of initiating therapy, not 6 years later. In addition, a corkscrew-shaped organism would not be seen on biopsy.

(Choice C) Fluroquinolones (eg, ciprofloxacin) disrupt bacterial DNA synthesis by blocking bacterial DNA gyrase and topoisomerase. Fluroquinolones are often used for gram-negative bacterial infections (eg, urinary tract infection) but not for syphilis.

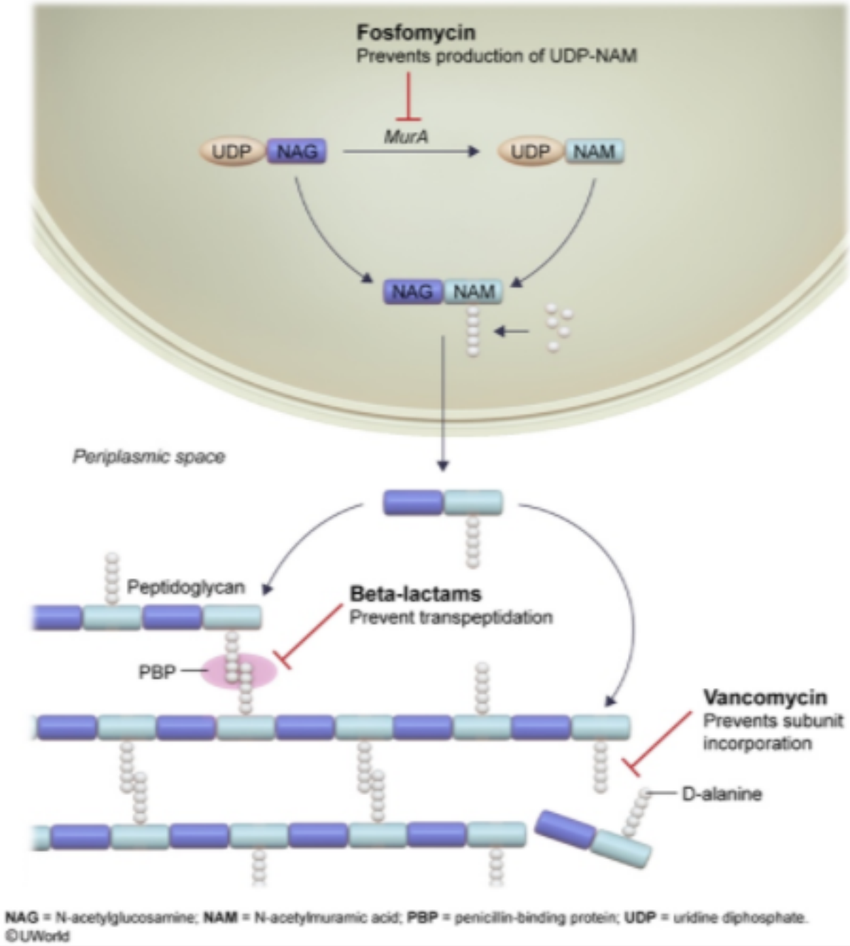
(Choice E) Trimethoprim-sulfamethoxazole disrupts bacterial folate metabolism by blocking enzymes that generate dihydrofolic and tetrahydrofolic acid. This agent is often used for urinary tract and skin/soft tissue infection but is not used for syphilis.

Educational objective:
Syphilis is caused by the corkscrew-shaped organism *Treponema pallidum*. Secondary syphilis develops in untreated patients weeks or months after the initial infection, and presents with a diffuse, macular rash and generalized lymphadenopathy. First-line treatment is penicillin, which blocks the last step in bacterial cell wall synthesis (transpeptidation).

The presence of a generalized rash, lymphadenopathy, and a **corkscrew-shaped organism** on histopathology suggests **secondary syphilis**, a

Exhibit Display

Antibiotics that inhibit cell wall synthesis



NAG = N-acetylglucosamine; NAM = N-acetylmuramic acid; PBP = penicillin-binding protein; UDP = uridine diphosphate.
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The presence of a generalized rash, lymphadenopathy, and a **corkscrew-shaped organism** on histopathology suggests **secondary syphilis**, a

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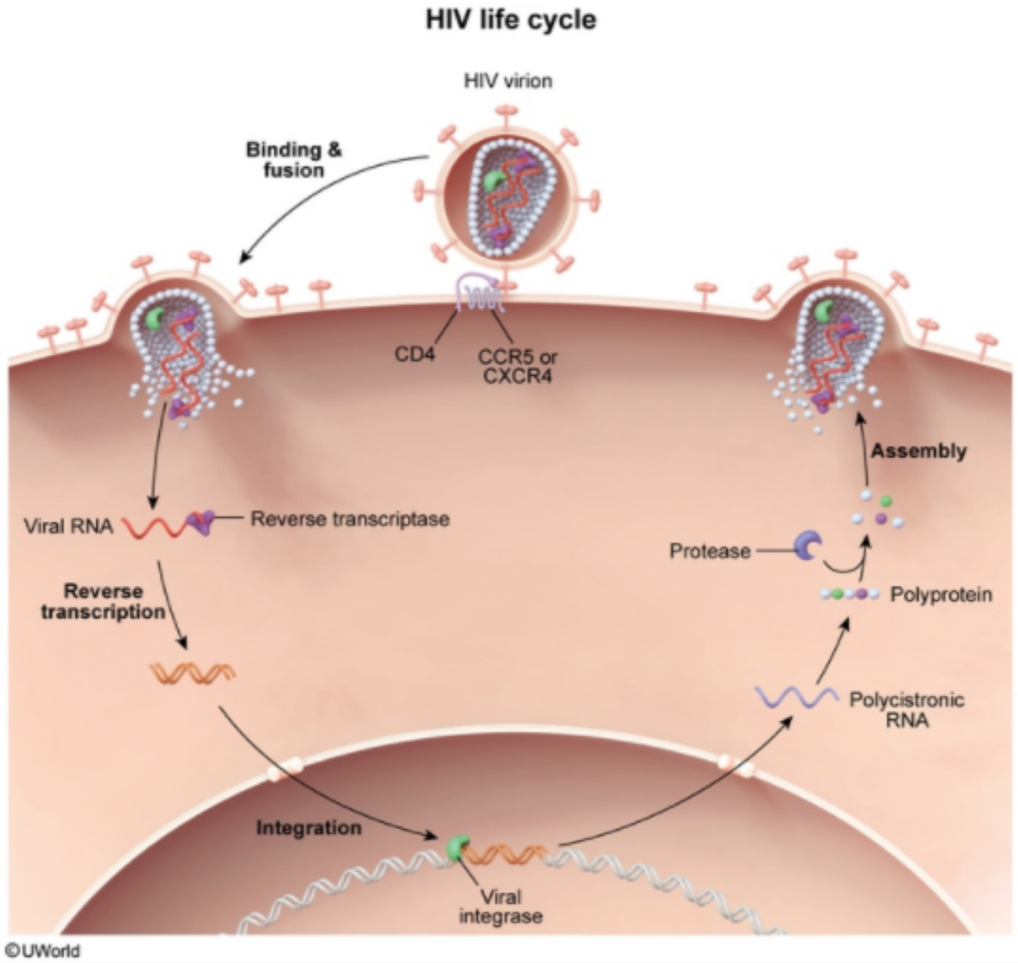

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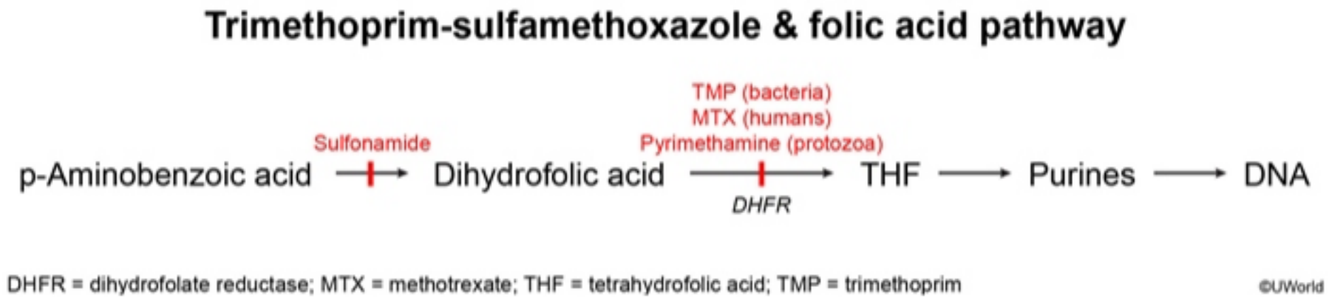

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Educational objective:
Syphilis is caused by the corkscrew-shaped organism *Treponema pallidum*. Secondary syphilis develops in untreated patients weeks or months after the initial infection, and presents with a diffuse, macular rash and generalized lymphadenopathy. First-line treatment is penicillin, which blocks the last step in bacterial cell wall synthesis (transpeptidation).

Pharmacology	Infectious Diseases	Syphilis
Subject	System	Topic

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A 64-year-old man comes to the emergency department due to fever, anorexia, and nausea. He recently immigrated to the United States to live with his son. Several weeks ago, on routine testing, the patient was found to have a positive purified protein derivative test. He had no respiratory symptoms, and a chest x-ray was unremarkable. A month ago, he started isoniazid therapy with pyridoxine supplementation. Currently, temperature is 38.3 C (100.9 F). On physical examination, there is mild abdominal discomfort. Laboratory studies are pending. Which of the following is the most likely cause of this patient's current symptoms?

- A. Factitious disorder
- B. Gastric mucosal damage
- C. Hepatocyte damage
- D. Peripheral nerve damage
- E. Serum sickness

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- A. Factitious disorder (1%)
- B. Gastric mucosal damage (8%)
- ✓ C. Hepatocyte damage (73%)
- D. Peripheral nerve damage (3%)
- E. Serum sickness (12%)

Omitted
Correct answer
C

73%
Answered correctly

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04/18/2020
Last Updated

Explanation

This patient with latent tuberculosis infection (positive tuberculin skin test, no symptoms, unremarkable chest x-ray) was started on **isoniazid** (INH) therapy and now has fever, anorexia, and nausea. INH is directly **hepatotoxic**. In 10%-20% of patients, it causes acute, **mild** hepatic dysfunction, characterized by transient increases in serum aminotransferases (AST/SGOT, ALT/SGPT). This adverse effect usually occurs during the first 4-6 months of treatment, and, in most cases, liver function tests return to baseline with continued INH therapy. In rare instances (<1%), frank **hepatitis** (similar to viral hepatitis with fever, anorexia, nausea, jaundice) can occur (as seen in this patient) and sometimes evolves into a

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(Choice A) Factitious disorder is the intentional falsification or inducement of symptoms with the goal of assuming the sick role. It is unlikely in this patient, who should be evaluated for INH hepatotoxicity.

(Choice B) Nonsteroidal anti-inflammatory drugs can cause gastric mucosal damage by inhibiting gastric prostaglandin production.

(Choice D) Peripheral neuropathy is also a potential side effect of INH therapy if simultaneous pyridoxine is not administered. However, peripheral neuropathy would not cause the above symptoms.

(Choice E) Serum sickness drug hypersensitivity generally causes fever, urticaria, arthralgias, proteinuria, and lymphadenopathy 5-10 days after exposure to the drug (antigen). This patient does not have arthralgias or skin findings.

Educational objective:
Isoniazid can be directly hepatotoxic, causing acute, mild hepatic dysfunction in 10%-20% of patients and frank hepatitis (fever, anorexia, and nausea, sometimes progressing to hepatic failure) in a small percentage of patients.

Pharmacology	Infectious Diseases	Tuberculosis
Subject	System	Topic

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A 45-year-old man comes to the office due to 3 months of night sweats, productive cough, decreased appetite, and a 5-kg (10-lb) weight loss. He travels frequently to Vietnam. Vital signs are normal. Examination reveals crackles in the right upper lobe of the lung. Chest x-ray reveals a right upper lobe infiltrate. Acid-fast bacilli are present on sputum smear. The patient is started on combination therapy with isoniazid, ethambutol, rifampin, pyrazinamide, and pyridoxine. One month later, he returns to the office reporting blurring of vision. Examination shows bilateral central scotomas. Which of the following is most likely responsible for this patient's visual symptoms?

A. Ethambutol
B. Isoniazid
C. Pyrazinamide
D. Pyridoxine
E. Rifampin

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- ✓ A. Ethambutol (75%)
- B. Isoniazid (11%)
- C. Pyrazinamide (5%)
- D. Pyridoxine (2%)
- E. Rifampin (4%)

Omitted
Correct answer
A

75%
Answered correctly

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Explanation

Drugs for treatment of tuberculosis		
Drug	**Mechanism of action**	**Side effects**
(R)ifampin	Inhibition of bacterial DNA-dependent RNA polymerase	GI side effects, rash, red-orange body fluids, cytopenias

Explanation

Drugs for treatment of tuberculosis		
Drug	**Mechanism of action**	**Side effects**
(R)ifampin	Inhibition of bacterial DNA-dependent RNA polymerase	GI side effects, rash, red-orange body fluids, cytopenias
(I)soniazid	Inhibition of mycolic acid synthesis	Neurotoxicity (give vitamin B_6/pyridoxine), hepatotoxicity
(P)yrazinamide	Unclear	Hepatotoxicity, hyperuricemia
(E)thambutol	Inhibition of arabinosyl transferase (?)	Optic neuropathy

GI = gastrointestinal.

This patient, who travels regularly to Vietnam and now has a cough, night sweats, and weight loss with a right upper lobe infiltrate on chest x-ray and acid-fast bacilli on sputum examination, likely has pulmonary **tuberculosis** (TB). Pulmonary TB is treated with a 4-drug regimen, sometimes referred to as RIPE: rifampin, isoniazid (INH), pyrazinamide, and ethambutol. The most notable side effect of **ethambutol** is **optic neuropathy**, which clinically manifests as decreased visual acuity, central scotoma, or color blindness. It may be reversible with discontinuation of the drug.

(Choices B and D) The most important side effect of INH is hepatotoxicity. INH is also associated with peripheral neuropathy, which is due to the drug's interference with pyridoxine metabolism and can be prevented by pyridoxine administration.

(Choice C) The most important side effects of pyrazinamide are hepatotoxicity and hyperuricemia (can exacerbate gout).

(Choice E) Rifampin can cause body fluids (eg, urine, tears) to turn red. This condition is benign.

Educational objective:
Ethambutol can cause optic neuropathy that results in color blindness, central scotoma, and decreased visual acuity. This adverse side effect may be reversed with discontinuation of the drug.

(R)ifampin	Inhibition of bacterial DNA-dependent RNA polymerase	GI side effects, rash, red-orange body fluids, cytopenias
(I)soniazid	Inhibition of mycolic acid synthesis	Neurotoxicity (give vitamin B_6/pyridoxine), hepatotoxicity
(P)yrazinamide	Unclear	Hepatotoxicity, hyperuricemia
(E)thambutol	Inhibition of arabinosyl transferase (?)	Optic neuropathy

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(Choice E) Rifampin can cause body fluids (eg, urine, tears) to turn red. This condition is benign.

Educational objective:
Ethambutol can cause optic neuropathy that results in color blindness, central scotoma, and decreased visual acuity. This adverse side effect may be reversed with discontinuation of the drug.

Pharmacology	Infectious Diseases	Tuberculosis
Subject	System	Topic

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A 30-year-old man comes to the emergency department due to a week of fever, chills, and generalized malaise. The patient uses intravenous heroin and has been hospitalized several times due to skin and soft tissue infections. Cardiac auscultation shows a systolic ejection murmur, and subsequent echocardiography reveals a vegetative lesion of the aortic valve. Blood cultures from admission grow *Enterococcus faecalis*; subsequent testing reveals D-lactate rather than D-alanine as the terminal amino acid in the bacteria's pentapeptide peptidoglycan cell wall precursor. This substitution is likely to significantly decrease the efficacy of which of the following antibiotics?

A. Ceftriaxone
B. Fosfomycin
C. Penicillin
D. Polymyxin
E. Tetracycline
F. Vancomycin

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A. Ceftriaxone (1%)
B. Fosfomycin (0%)
C. Penicillin (12%)
D. Polymyxin (0%)
E. Tetracycline (0%)
✓ F. Vancomycin (85%)

Omitted
Correct answer
F

85%
Answered correctly

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Time Spent

03/16/2020
Last Updated

Explanation

Antibiotics that inhibit cell wall synthesis

Fosfomycin
Prevents production of UDP-NAM

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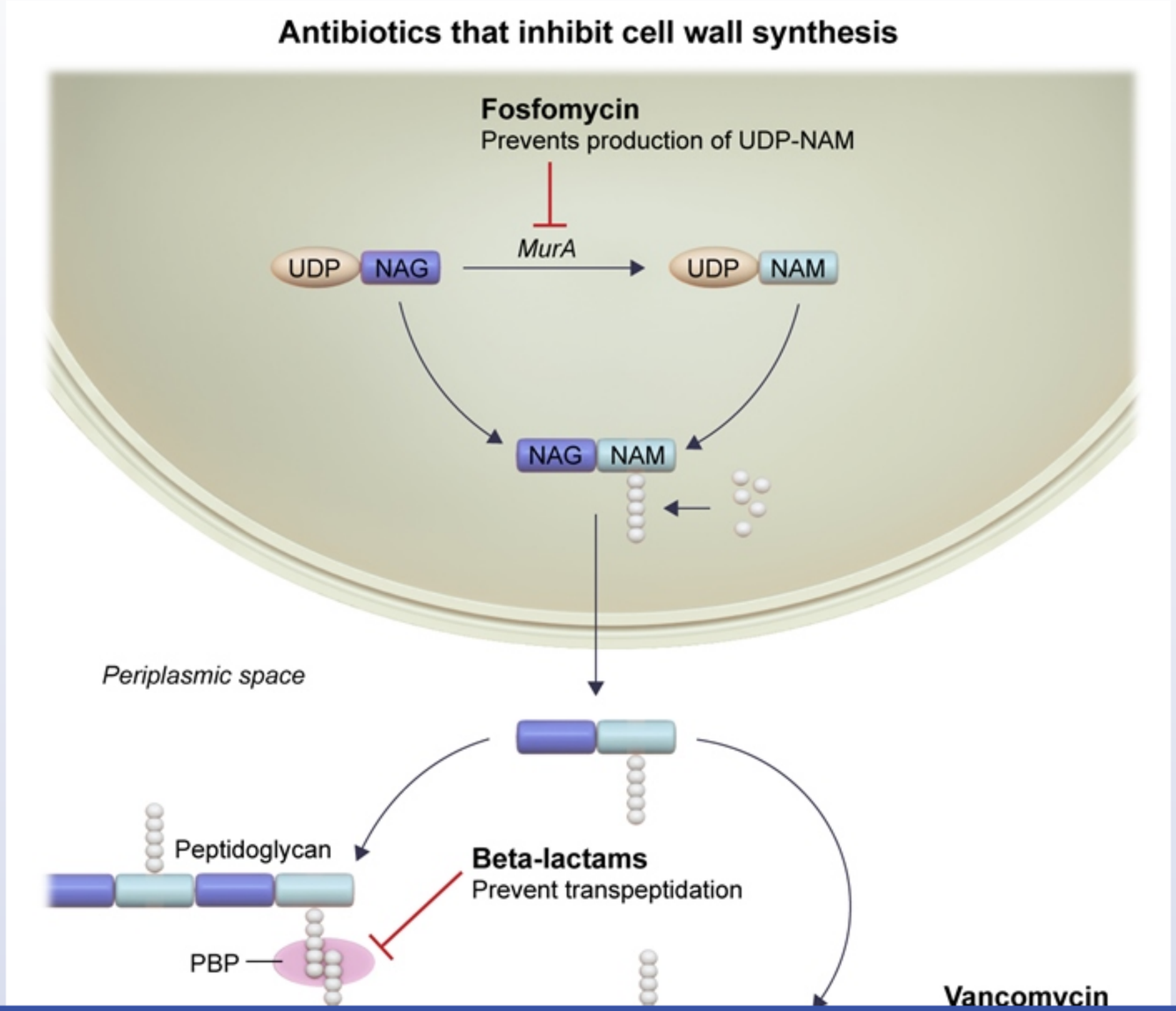

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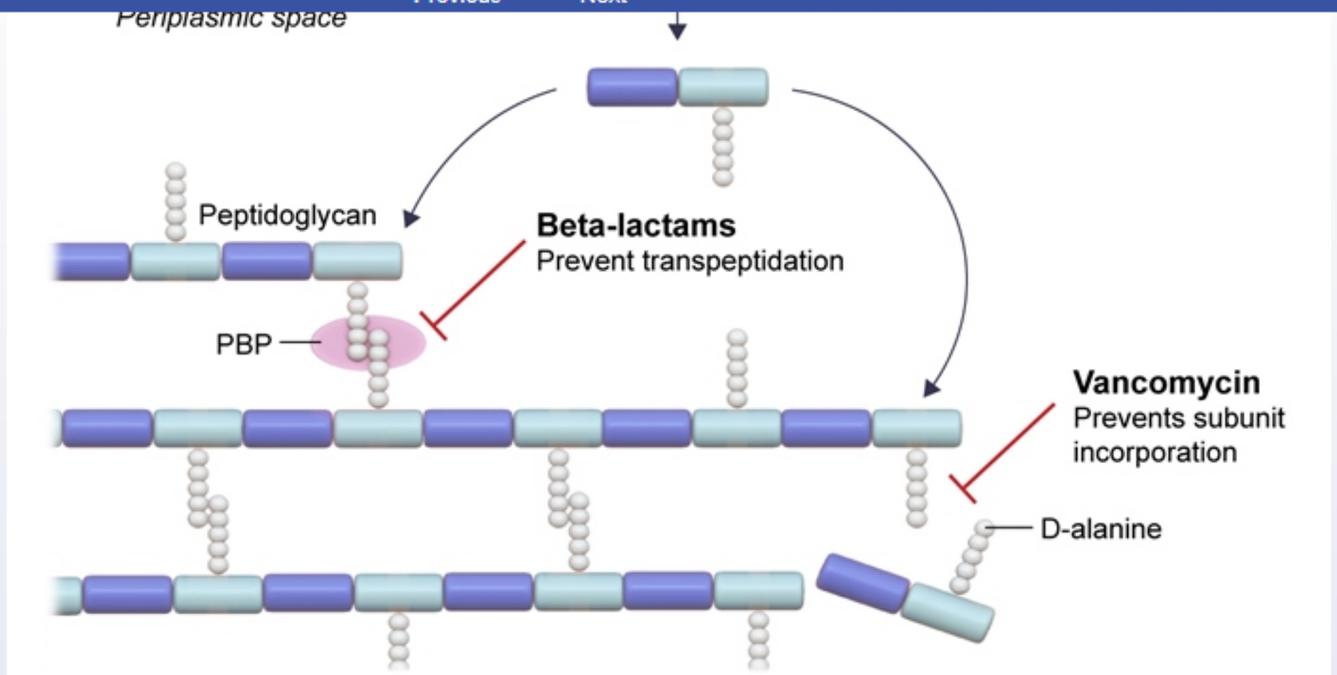

NAG = N-acetylglucosamine; **NAM** = N-acetylmuramic acid; **PBP** = penicillin-binding protein; **UDP** = uridine diphosphate.
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The bacterial cell wall is composed of cross-linked **peptidoglycan subunits** on a backbone of N-acetylmuramic acid (NAM) and N-acetylglucosamine (NAG). Because cell wall disruption results in bacterial lysis, many antibiotics target cell wall synthesis, including the following:

- **Fosfomycin** blocks development of the NAM-NAG polymer backbone by inhibiting the enzyme MurA. Resistance stems primarily from efflux pumps or alterations to MurA that prevent fosfomycin binding **(Choice B)**.

- **Vancomycin** inhibits transpeptidase from cross linking a growing peptidoglycan chain by binding to the **D-alanine–D-alanine terminus** of pentapeptide peptidoglycan subunits. **Resistance to vancomycin** stems primarily from replacement of the terminal D-alanine–D-alanine with **D-alanine–D-lactate,** which reduces vancomycin binding >1000-fold.

- **Penicillin and cephalosporins** (eg, ceftriaxone) are beta-lactam antibiotics that bind to and directly inhibit transpeptidase. Resistance

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- **Penicillin and cephalosporins** (eg, ceftriaxone) are beta-lactam antibiotics that bind to and directly inhibit transpeptidase. Resistance stems primarily from alterations to transpeptidase that reduce beta-lactam binding or the production of enzymes (eg, penicillinase) that break down the drug **(Choices A and C)**.

(Choice D) Polymyxin binds to lipopolysaccharide, leading to disruption of the bacterial cytoplasmic membrane. It does not interfere with the bacterial cell wall.

(Choice E) Tetracycline binds to the 30S ribosomal subunit and prevents binding of aminoacyl–transfer RNAs. Resistance stems primarily from an efflux pump or alteration to the ribosome that allows translation to take place even when tetracycline is present.

Educational objective:
Vancomycin binds to the terminal D-alanine–D-alanine in bacterial pentapeptide peptidoglycan subunits, which prevents transpeptidase from binding to the pentapeptide, thereby inhibiting cell wall cross-linking. Resistance stems primarily from substitution of the terminal D-alanine with D-lactate, which prevents vancomycin binding.

References

- Vancomycin-resistant enterococci.
- Antibiotic resistance in bacteria and its future for novel antibiotic development.

Pharmacology Infectious Diseases Antibiotic resistance

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A 78-year-old woman comes to the office due to fever, headache, sore throat, cough, and severe myalgias for 24 hours. Her medical problems include hypertension and Alzheimer dementia. Her family came to visit over the weekend, and her grandson had symptoms of a cold. The patient's temperature is 38.9 C (102 F). Lung examination is unremarkable. A nasal specimen swab is positive for influenza. The patient is started on oseltamivir. Which of the following is most likely impaired in the patient's infected cells as a result of the treatment?

- A. Foreign protein splitting
- B. Foreign protein synthesis
- C. Viral RNA replication
- D. Viral uncoating
- E. Virion particle release

Submit

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- A. Foreign protein splitting (2%)
- B. Foreign protein synthesis (3%)
- C. Viral RNA replication (12%)
- D. Viral uncoating (13%)
- ✓ E. Virion particle release (67%)

Omitted
Correct answer
E

67%
Answered correctly

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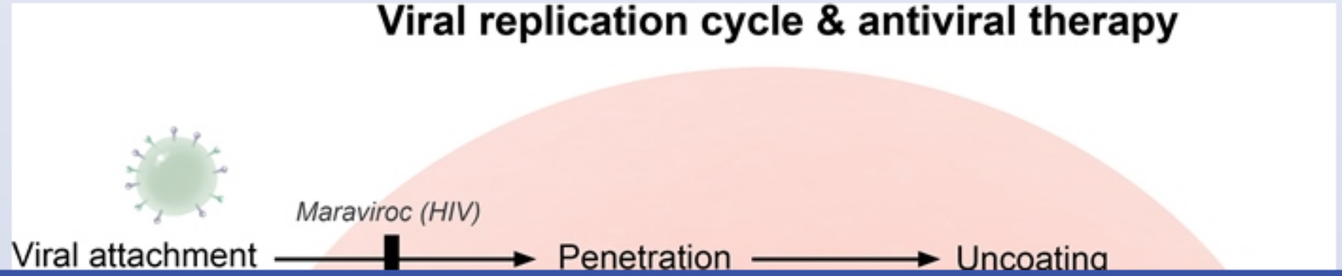
Time Spent

04/12/2020
Last Updated

Explanation



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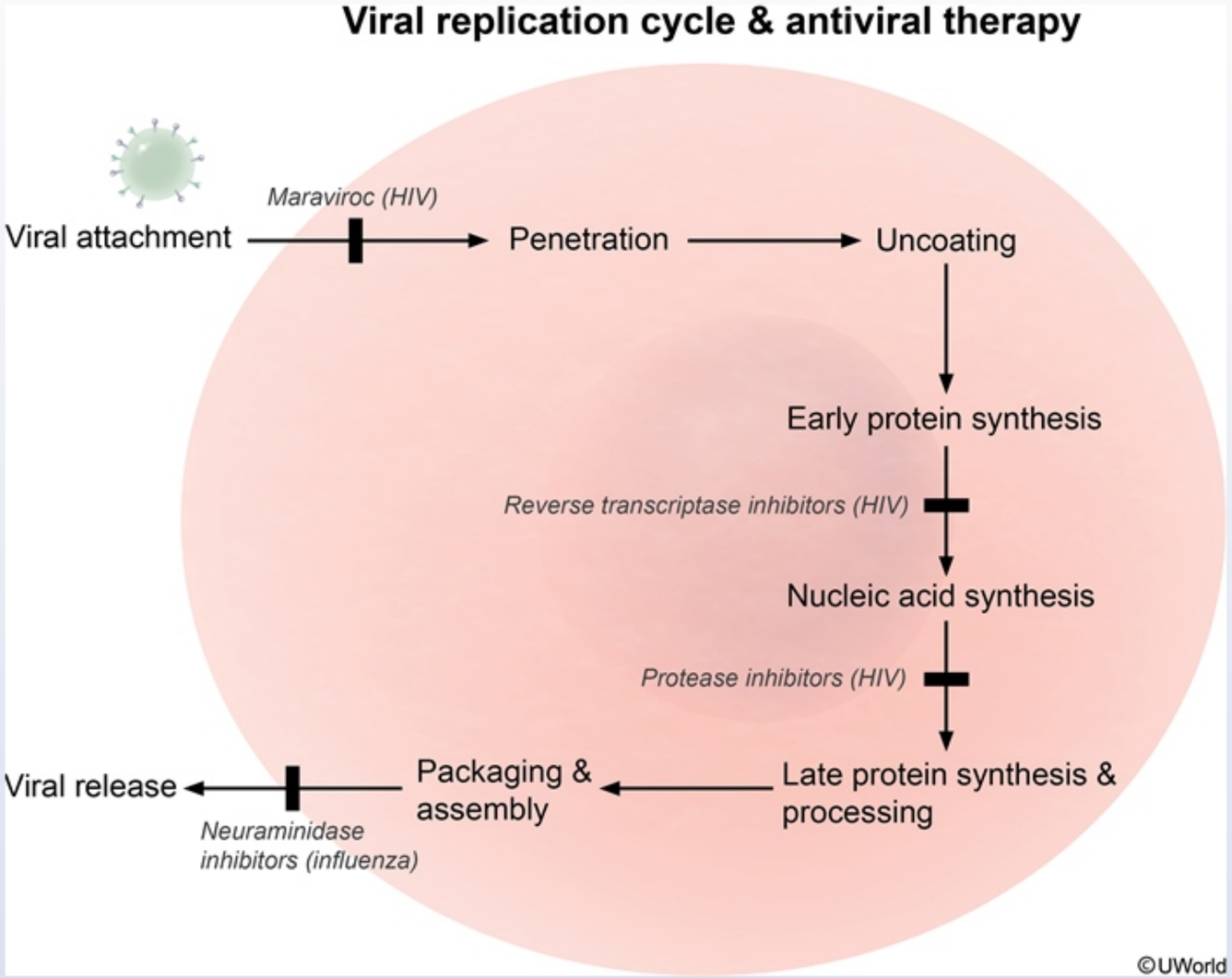

Oseltamivir is a **neuraminidase inhibitor** useful in the treatment of both influenza A and B virus infections. Neuraminidase is required for the **release** of virus from infected cells and for the spread of virus within the respiratory tract. Neuraminidase inhibitors cause the newly synthesized

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Oseltamivir is a **neuraminidase inhibitor** useful in the treatment of both influenza A and B virus infections. Neuraminidase is required for the **release** of virus from infected cells and for the spread of virus within the respiratory tract. Neuraminidase inhibitors cause the newly synthesized virions to adhere to the host cell surface and form viral aggregates, thereby reducing the spread of virus to other host cells. Oseltamivir (Tamiflu) can shorten the course and complications of influenza A and B infections if taken within 48 hours of the onset of symptoms. In addition, oseltamivir works to slow viral penetration of the mucous secretions that protect the respiratory epithelium. Oseltamivir can therefore be used to treat or prevent influenza.

(Choice A) The influenza viral genome consists of segmented RNA, which is translated predominantly into individual proteins rather than a large polyprotein product. HIV protease inhibitors (eg, darunavir) are used to counteract HIV polyprotein cleavage mediated by viral protease.

(Choice B) Foreign (viral) protein synthesis can be inhibited by α- and β-interferons, which induce the synthesis of proteins that have an antiviral effect. These antiviral proteins promote the degradation of RNA and halt protein translation in virally infected cells only.

(Choice C) Impairment of viral RNA replication is accomplished by the reverse transcriptase inhibitors used to combat HIV (eg, abacavir, tenofovir, zidovudine).

(Choice D) Amantadine (limited use in influenza management due to viral resistance) impairs uncoating or disassembly of the influenza A virion after host cell endocytosis. Oseltamivir does not operate via the same mechanism of action. Currently, amantadine is mainly used in Parkinson disease as it increases dopamine release (unclear mechanism).

Educational objective:
Oseltamivir is a neuraminidase inhibitor useful in the treatment and prevention of both influenza A and B virus infections. This medication impairs the release of newly formed virions from infected host cells and impairs viral penetration of mucous secretions that overlie the respiratory epithelium.

Pharmacology	Infectious Diseases	Influenza
Subject	System	Topic

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A 31-year-old man comes to the emergency department with a 2-week history of fever, night sweats, and productive cough. He has also had a 5-kg (11-lb) weight loss. He has no other medical problems. The patient is a software engineer who moved to the United States from Uzbekistan 15 years ago. He takes no medications and has no known drug allergies. His temperature is 38.3 C (101 F), blood pressure is 110/80 mm Hg, pulse is 94/min, and respirations are 18/min. He weighs 60 kg (132.3 lb). Pulse oximetry shows 94% on room air. Chest-x ray reveals a cavitary lesion on the right. Sputum culture is obtained. When exposed to drug A, isolates of the pathogen growing in culture quickly become less resistant to decoloration with an acid-alcohol agent and stop proliferating. Which of the following is drug A most likely to be?

- A. Ciprofloxacin
- B. Isoniazid
- C. Rifampin
- D. Streptomycin
- E. Vancomycin

Submit

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- A. Ciprofloxacin (1%)
- ✓ B. Isoniazid (72%)
- C. Rifampin (20%)
- D. Streptomycin (3%)
- E. Vancomycin (2%)

Omitted
Correct answer
B

72%
Answered correctly

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Last Updated

Explanation

Drugs for treatment of tuberculosis		
Drug	**Mechanism of action**	**Side effects**
	Inhibition of bacterial	GI side effects, rash,

Drugs for treatment of tuberculosis		
Drug	**Mechanism of action**	**Side effects**
(R)ifampin	Inhibition of bacterial DNA-dependent RNA polymerase	GI side effects, rash, red-orange body fluids, cytopenias
(I)soniazid	Inhibition of mycolic acid synthesis	Neurotoxicity (give vitamin B_6/pyridoxine), hepatotoxicity
(P)yrazinamide	Unclear	Hepatotoxicity, hyperuricemia
(E)thambutol	Inhibition of arabinosyl transferase (?)	Optic neuropathy

GI = gastrointestinal.

Isoniazid is an antimicrobial agent that is active only against mycobacteria. Its specificity is derived from its **inhibition of mycolic acid synthesis**. Mycolic acids form long branched-chain fatty acids in the outer portion of the mycobacterial peptidoglycan cell wall; they are essential for proper **cell wall** structure and virulence factor synthesis (eg, sulfatides, wax D, cord factor). If mycobacteria are unable to synthesize mycolic acids, they cannot create proper cell walls or divide to form new cells. Mycolic acids in the cell wall cause mycobacteria to be **acid-fast** as they retain the carbolfuchsin dye and resist decoloration by an acid-alcohol decolorizing agent.

(Choice A) The fluoroquinolones (eg, ciprofloxacin) are emerging as new components of the multi-drug regimen used to treat tuberculosis. They inhibit DNA gyrase, leading to fractures in the bacterial chromosome and an inability to code for proteins necessary for survival. Fluoroquinolones would not have an immediate effect on the acid-fastness of mycobacteria.

(Choice C) Rifampin is an essential component of the multi-drug regimen used to treat active tuberculosis. Rifampin halts bacterial protein synthesis by inhibiting bacterial DNA-dependent RNA polymerase, thereby preventing DNA transcription into mRNA. Rifampin would inhibit mycobacterial growth in an in vitro culture, but it would not cause the mycobacteria to lose their acid-fastness.

(Choice D) Streptomycin is an aminoglycoside that inhibits the bacterial 30S (small) ribosomal subunit, thereby halting protein synthesis. Mycobacterial cell growth is restricted and eventually cell death results. However, the acid-fastness of the organism is not affected. Streptomycin

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(Choice E) Vancomycin binds to D-alanyl-D-alanine residues, inhibiting polymerization and cross-linking of the glycopeptides forming the cell wall of gram-positive bacteria (not mycobacteria).

Educational objective:
Isoniazid is an antimycobacterial agent that specifically inhibits the synthesis of mycolic acids, which are essential components of the unique mycobacterial peptidoglycan cell wall. Without mycolic acids, the mycobacteria lose their acid-fastness and become unable to synthesize new cell walls or multiply.

References

- Drugs that inhibit mycolic acid biosynthesis in Mycobacterium tuberculosis.

Pharmacology Infectious Diseases Tuberculosis

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Pharmacology	Infectious Diseases	Tuberculosis
Subject	System	Topic

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Researchers analyze the HIV viral structure and replication cycle for new drug targets. They find the virus encodes a large glycoprotein, which gets cleaved into 2 subunits, the surface and transmembrane subunits. These subunits remain noncovalently bound to each other in the virion. Upon activation of the surface protein, conformational changes occur in the transmembrane subunit exposing the functional inner core. A novel drug is developed that selectively binds and prevents normal functioning of the transmembrane subunit, interfering with the normal viral replication cycle. This agent most likely directly inhibits which of the following viral processes?

- A. Attachment of the virus to target cell surface
- B. Budding and release of a new virus particle
- C. Cleavage of polyproteins by viral encoded enzyme
- D. Entry of the viral core into host cytoplasm
- E. Integration of the viral DNA into host genome
- F. Synthesis of DNA from viral RNA template
- G. Transcription of mRNA from proviral DNA

Submit

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- A. Attachment of the virus to target cell surface (20%)
- B. Budding and release of a new virus particle (4%)
- C. Cleavage of polyproteins by viral encoded enzyme (4%)
- ✓ D. Entry of the viral core into host cytoplasm (57%)
- E. Integration of the viral DNA into host genome (7%)
- F. Synthesis of DNA from viral RNA template (3%)
- G. Transcription of mRNA from proviral DNA (1%)

Omitted
Correct answer
D

57%
Answered correctly

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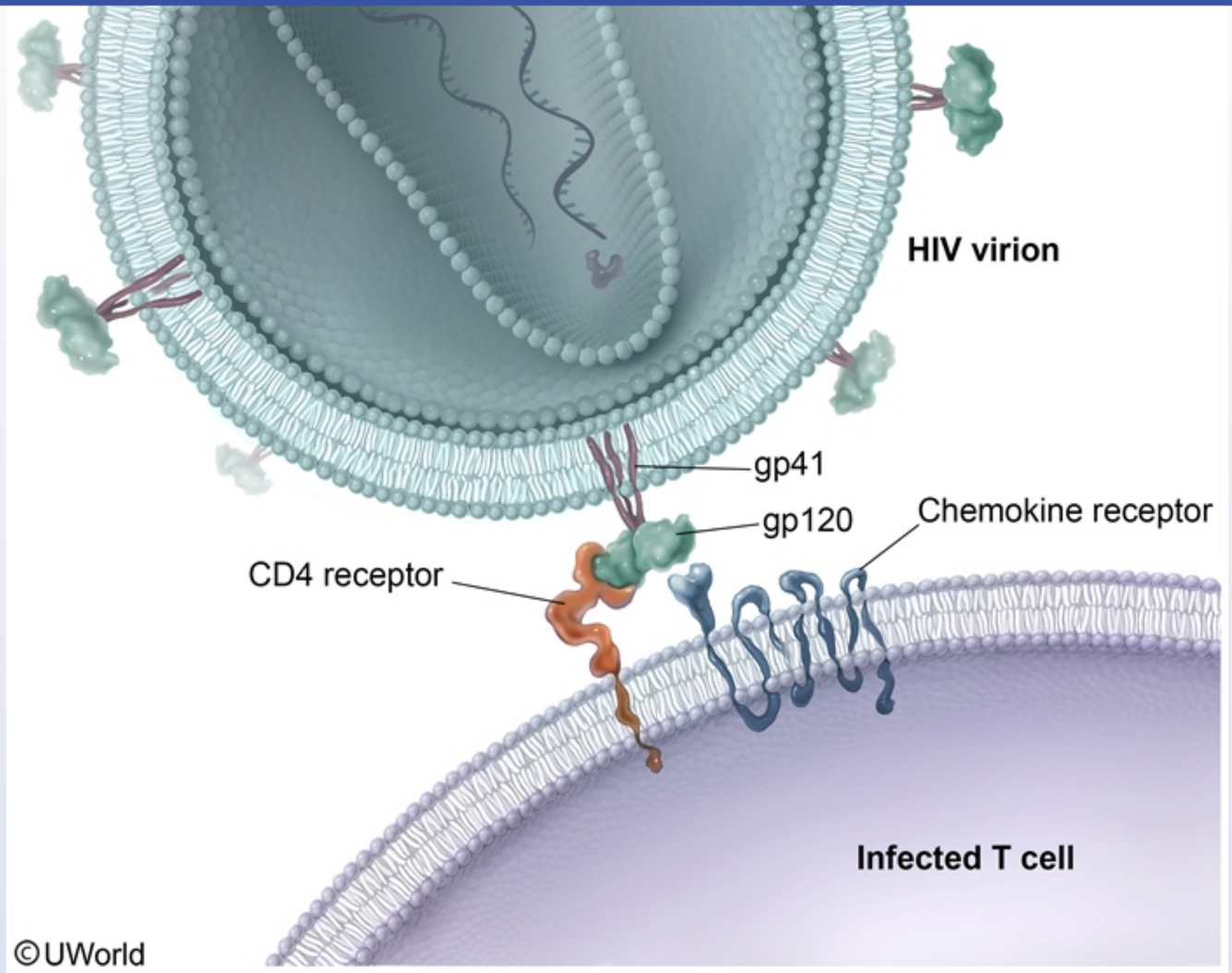
04/11/2020
Last Updated

Explanation



The HIV genome encodes several enzymes and structural proteins in polycistronic mRNAs that are then translated into polyproteins and cleaved by proteases into the individual proteins that compose the virus. The *env* gene encodes the **polyprotein gp160**, which is extensively **glycosylated** in the endoplasmic reticulum and Golgi body and subsequently cleaved into the mature envelope proteins gp120 and gp41. These

The HIV genome encodes several enzymes and structural proteins in polycistronic mRNAs that are then translated into polyproteins and cleaved by proteases into the individual proteins that compose the virus. The *env* gene encodes the **polyprotein gp160**, which is extensively **glycosylated** in the endoplasmic reticulum and Golgi body and subsequently cleaved into the mature envelope proteins gp120 and gp41. These envelope proteins remain associated by noncovalent attachments and form the **glycoprotein spikes** that pepper the surface of the HIV virus.

gp120 forms the outside surface of the glycoprotein spike and **mediates viral attachment** to the host cell by binding with the CD4 receptor and a chemokine coreceptor (CXCR4, CCR5) **(Choice A)**. Binding of gp120 to these host receptors induces a conformational change in the structure of the glycoprotein spike that exposes the underlying transmembrane glycoprotein gp41. **gp41 mediates fusion** of the viral cell membrane with the host cell membrane, thereby allowing the **viral core to enter the cell**.

Drugs that selectively bind gp41 (eg, enfuvirtide) are known as **fusion inhibitors** because they prevent gp41 from undergoing the conformational changes necessary for viral fusion, which prevents the HIV genome from entering uninfected cells.

(Choice B) Viral assembly and budding occur at the cell surface. The envelope proteins (gp120, gp41) are expressed on the cell surface and then a complex of the nucleocapsid, viral RNA, and viral proteins (gag and pol polyproteins) bud from the surface. Further assembly then occurs when the virus is free from the host cell. The transmembrane gp41 does not catalyze the budding or assembly process.

(Choice C) Protease is an HIV enzyme that mediates the cleavage of HIV polyproteins into the individual proteins that compose the HIV virus. Protease inhibitors (eg, atazanavir, darunavir) block the action of this enzyme.

(Choice E) Integrase inserts the viral double-stranded DNA into the host genome. Inte*grase* inhibitors (eg, ralte*gravir*, dolute*gravir*) are often part of first-line therapy for HIV.

(Choice F) Reverse transcriptase converts viral single-stranded RNA into complementary double-stranded DNA. Reverse transcriptase inhibitors terminate viral DNA elongation by competitive or allosteric inhibition.

(Choice G) Host RNA polymerase II transcribes proviral DNA into mRNA, which is then translated in the rough endoplasmic reticulum.

Educational objective:
Fusion inhibitors (eg, enfuvirtide) bind the HIV transmembrane glycoprotein gp41 and prevent it from approximating the viral and host cellular membranes, which prevents HIV penetration into new host cells.

References

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References

- HIV-1 envelope glycoprotein biosynthesis, trafficking, and incorporation

Pharmacology	Infectious Diseases	Antiretroviral therapy
Subject	System	Topic

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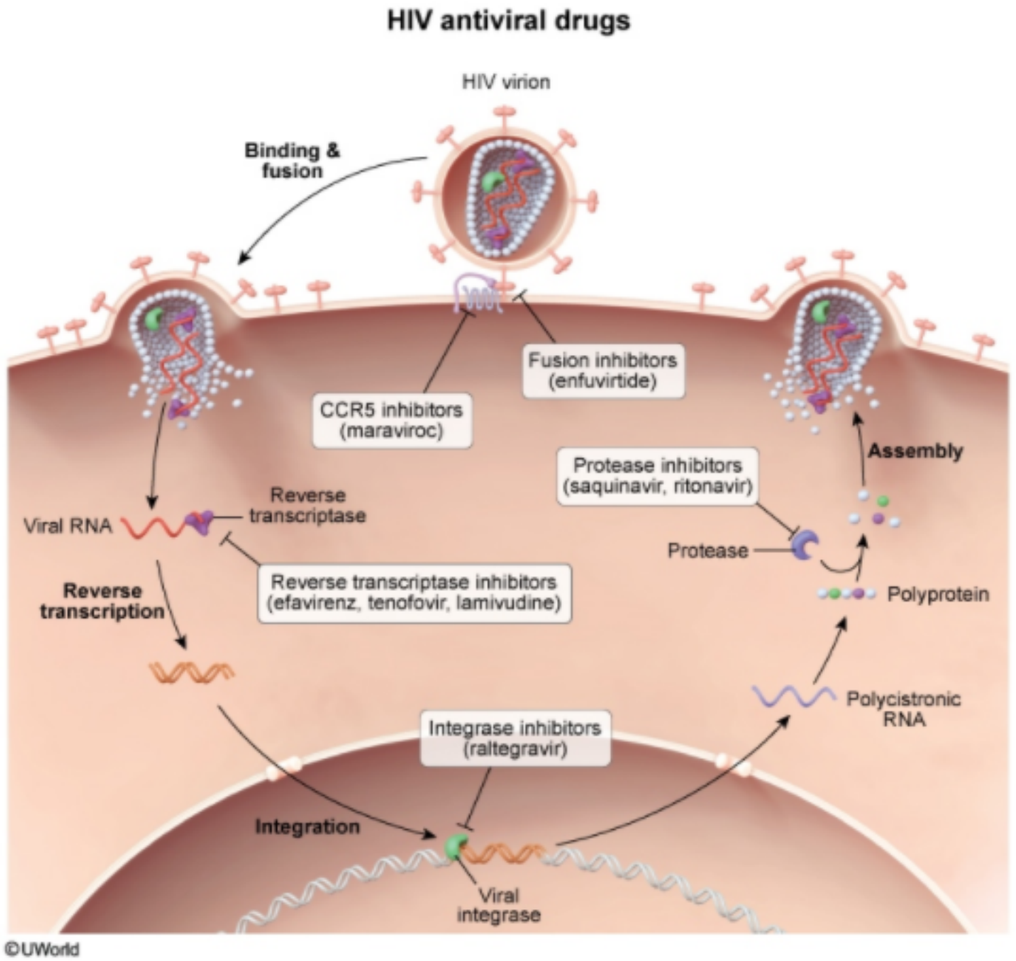
Infected T cell

Exhibit Display



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Educational objective:

A 70-year-old man is diagnosed with a pulmonary nocardia infection. Medical conditions include hypertension and diet-controlled type 2 diabetes mellitus. Therapy is started with trimethoprim-sulfamethoxazole for a planned duration of 3-6 months. This patient is at greatest risk for which of the following drug-induced adverse effects?

- A. Esophagitis
- B. Hearing loss
- C. Hyperkalemia
- D. Pulmonary fibrosis
- E. Tendon rupture

Submit

A 70-year-old man is diagnosed with a pulmonary nocardia infection. Medical conditions include hypertension and diet-controlled type 2 diabetes mellitus. Therapy is started with trimethoprim-sulfamethoxazole for a planned duration of 3-6 months. This patient is at greatest risk for which of the following drug-induced adverse effects?

- A. Esophagitis (11%)
- B. Hearing loss (8%)
- ✓ C. Hyperkalemia (67%)
- D. Pulmonary fibrosis (7%)
- E. Tendon rupture (4%)

Omitted
Correct answer
C

67%
Answered correctly

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Time Spent

04/30/2020
Last Updated

Explanation

Trimethoprim-sulfamethoxazole (TMP-SMX) is a combination of 2 bacteriostatic antibiotics that act synergistically to inhibit bacterial tetrahydrofolate formation, resulting in bactericidal activity. It has a broad spectrum of activity against many aerobic gram-positive and gram-negative bacteria and is commonly used for urinary tract infections, *Pneumocystis jiroveci* pneumonia, and *Nocardia* infections.

Common adverse effects of TMP-SMX include rash, nausea and vomiting, and folate deficiency (with prolonged use). In addition, **hyperkalemia** is a common adverse effect that can occur, regardless of dose. Similar to the actions of amiloride (a potassium-sparing diuretic), trimethoprim **blocks** the epithelial **sodium channel** in the distal tubule and collecting duct. This reduces transepithelial voltage and **impairs sodium-potassium exchange**, leading to reduced potassium excretion and hyperkalemia.

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This effect is often magnified in the **elderly** population, those with renal failure, or those given other **potassium-sparing diuretics** (eg, spironolactone, amiloride), **ACE inhibitors** (eg, lisinopril), or angiotensin receptor blockers (eg, losartan). This patient with hypertension and diabetes may be receiving an ACE inhibitor, which further increases his risk of developing hyperkalemia.

(Choice A) Tetracyclines (eg, doxycycline, minocycline) and clindamycin are associated with esophagitis due to their low pH and irritant effects on the distal esophagus.

(Choice B) Aminoglycosides (eg, gentamycin, tobramycin) have broad-spectrum activity against aerobic gram-negative organisms and are most often used in severe gram-negative infections (eg, intraabdominal infections, osteomyelitis). These medications are associated with ototoxicity and may lead to tinnitus and hearing loss.

(Choice D) Nitrofurantoin has activity against many gram-positive and gram-negative urinary tract pathogens and is used for both acute treatment of urinary tract infections and long-term prophylaxis in patients with recurrent cystitis. It is associated with pneumonitis and pulmonary fibrosis.

(Choice E) Fluoroquinolones (eg, levofloxacin, ciprofloxacin) have activity against aerobic gram-negative rods and many respiratory pathogens. They are commonly used to treat pneumonia, pseudomonal infections, and urinary tract infections. These medications are associated with tendinopathy, including tendon rupture.

Educational objective:
Hyperkalemia is a common adverse effect of trimethoprim-sulfamethoxazole due to the trimethoprim-induced blockade of the sodium channels in the collecting duct, which prevents sodium-potassium exchange and reduces renal excretion of potassium (similar to the action of amiloride). This effect is often magnified in the elderly population, those with renal failure, or those given other potassium-sparing diuretics, ACE inhibitors, or

blocks the epithelial **sodium channel** in the distal tubule and collecting duct. This reduces transepithelial voltage and **impairs sodium-potassium exchange**, leading to reduced potassium excretion and hyperkalemia.

This effect is often magnified in the **elderly** population, those with renal failure, or those given other **potassium-sparing diuretics** (eg, spironolactone, amiloride), **ACE inhibitors** (eg, lisinopril), or angiotensin receptor blockers (eg, losartan). This patient with hypertension and diabetes may be receiving an ACE inhibitor, which further increases his risk of developing hyperkalemia.

(Choice A) Tetracyclines (eg, doxycycline, minocycline) and clindamycin are associated with esophagitis due to their low pH and irritant effects on the distal esophagus.

(Choice B) Aminoglycosides (eg, gentamycin, tobramycin) have broad-spectrum activity against aerobic gram-negative organisms and are most often used in severe gram-negative infections (eg, intraabdominal infections, osteomyelitis). These medications are associated with ototoxicity and may lead to tinnitus and hearing loss.

(Choice D) Nitrofurantoin has activity against many gram-positive and gram-negative urinary tract pathogens and is used for both acute treatment of urinary tract infections and long-term prophylaxis in patients with recurrent cystitis. It is associated with pneumonitis and pulmonary fibrosis.

(Choice E) Fluoroquinolones (eg, levofloxacin, ciprofloxacin) have activity against aerobic gram-negative rods and many respiratory pathogens. They are commonly used to treat pneumonia, pseudomonal infections, and urinary tract infections. These medications are associated with tendinopathy, including tendon rupture.

Educational objective:
Hyperkalemia is a common adverse effect of trimethoprim-sulfamethoxazole due to the trimethoprim-induced blockade of the sodium channels in the collecting duct, which prevents sodium-potassium exchange and reduces renal excretion of potassium (similar to the action of amiloride). This effect is often magnified in the elderly population, those with renal failure, or those given other potassium-sparing diuretics, ACE inhibitors, or angiotensin receptor blockers.

Pharmacology	Infectious Diseases	Hyperkalemia
Subject	System	Topic

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A 25-year-old man comes to the office for follow-up. He was diagnosed with HIV several weeks ago following a hospitalization for *Pneumocystis* pneumonia. He has no other medical problems. His HIV drug susceptibility report shows no evidence of resistance. The patient's treatment regimen includes a drug that is structurally unrelated to nucleosides and is not phosphorylated intracellularly. The drug acts within the cytoplasm of infected cells to inhibit the synthesis of viral DNA from the RNA template. Which of the following agents was most likely used in this patient?

A. Emtricitabine
B. Enfuvirtide
C. Nevirapine
D. Ritonavir
E. Zidovudine

Submit

A 25-year-old man comes to the office for follow-up. He was diagnosed with HIV several weeks ago following a hospitalization for *Pneumocystis* pneumonia. He has no other medical problems. His HIV drug susceptibility report shows no evidence of resistance. The patient's treatment regimen includes a drug that is structurally unrelated to nucleosides and is not phosphorylated intracellularly. The drug acts within the cytoplasm of infected cells to inhibit the synthesis of viral DNA from the RNA template. Which of the following agents was most likely used in this patient?

A. Emtricitabine (8%)
B. Enfuvirtide (12%)
✓ C. Nevirapine (37%)
D. Ritonavir (20%)
E. Zidovudine (20%)

Omitted
Correct answer
C

37%
Answered correctly

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Explanation

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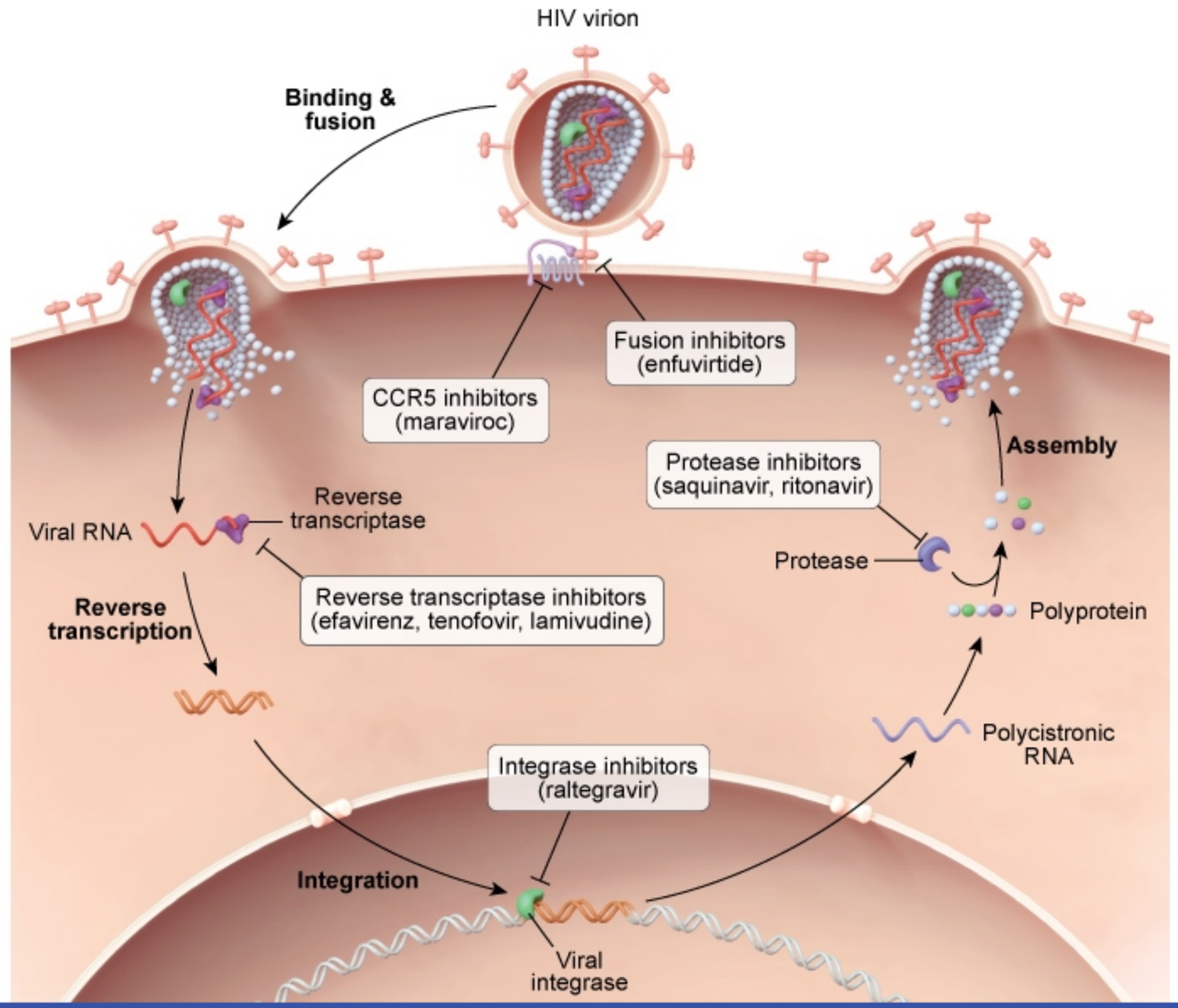
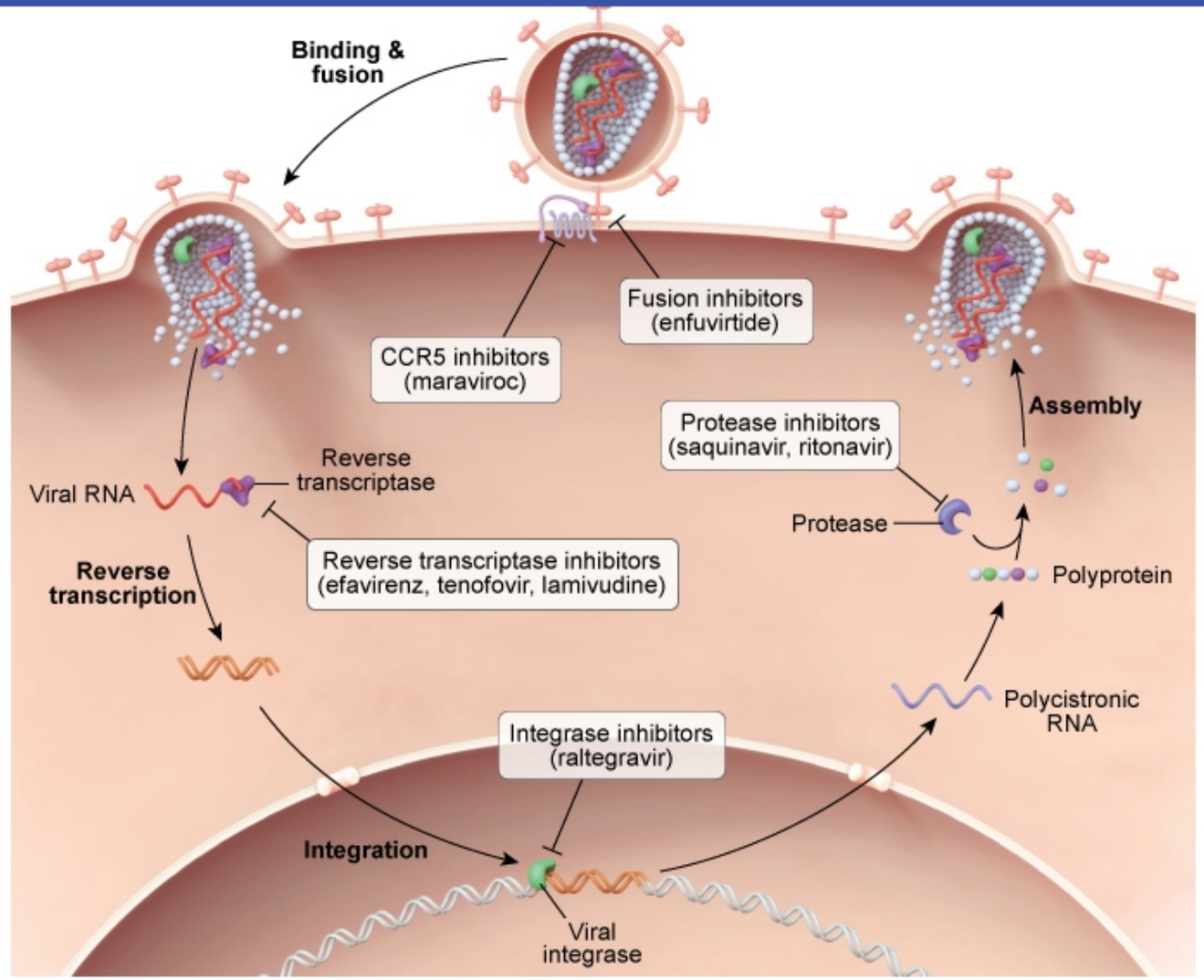
HIV antiviral drugs





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Retroviral reverse transcriptase inhibitors prevent the synthesis of viral DNA from the RNA template. **Nonnucleoside reverse transcriptase inhibitors** (NNRTIs) do **not** require activation via intracellular phosphorylation. The more common NNRTIs include **nevirapine** and **efavirenz**.

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Retroviral reverse transcriptase inhibitors prevent the synthesis of viral DNA from the RNA template. **Nonnucleoside reverse transcriptase inhibitors** (NNRTIs) do **not** require activation via intracellular phosphorylation. The more common NNRTIs include **nevirapine** and **efavirenz**. They are best used in conjunction with other antiretroviral agents for the treatment of HIV infection.

Adverse effects are common with NNRTIs. Abrupt-onset flulike symptoms, abdominal pain, jaundice, or fever may indicate potentially life-threatening **hepatic failure** (most likely to occur within the first 6 weeks of NNRTI therapy). Life-threatening skin reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis) have also been observed.

(Choices A and E) Zidovudine and emtricitabine are nucleoside reverse transcriptase inhibitors (NRTIs). In general, NRTIs must be converted into their monophosphate forms by a cellular kinase (cellular thymidine kinase) before they can be converted into pharmacologically active triphosphate forms.

(Choice B) Enfuvirtide is an HIV fusion inhibitor that binds to HIV envelope gp41 and blocks the conformational changes necessary for the fusion of viral and cellular membranes. Through this mechanism, enfuvirtide denies the HIV genome entry into uninfected $CD4^+$ T-cells. Its main site of action is outside the cytoplasm.

(Choice D) Ritonavir is an inhibitor of HIV protease that prevents assembly and maturation of the virus. Nonfunctional, noninfectious virions are produced instead. Reverse transcription is not affected.

Educational objective:
Nonnucleoside reverse transcriptase inhibitors (NNRTIs) are antiretroviral drugs that do not require activation via intracellular phosphorylation. The more common NNRTIs include nevirapine and efavirenz.

Pharmacology	Infectious Diseases	Antiretroviral therapy
Subject	System	Topic

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Retroviral reverse transcri
inhibitors (NNRTIs) do n
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(Choice B) Enfuvirtide is
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(Choice D) Ritonavir is a
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Educational objective:
Nonnucleoside reverse tra
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Mechanism of action of HIV antiretroviral medications

Class	Example(s)	Mechanism of action
NRTI	Tenofovir, emtricitabine, lamivudine, abacavir, zidovudine	Inhibits HIV DNA synthesis from RNA template by terminating DNA chain elongation • NRTI: **Competitive** nucleoside/nucleotide RT inhibitor • NNRTI: **Allosteric** RT inhibitor
NNRTI	Efa**vir**enz, ne**vir**apine	
PI	Ataza**navir**, daru**navir**, indi**navir**, rito**navir**	Inhibits HIV polyprotein **cleavage**
Inte**grase** inhibitor	Dolute**gravir**, ralte**gravir**	Inhibits HIV DNA integration into host genome
Fusion inhibitor	En**fu**virtide	Inhibits HIV fusion with target cell membrane by binding to HIV **gp41**
CCR5 antagonist	Maraviroc	Inhibits HIV entry by blocking the HIV **gp120 allosteric** interaction with CCR5 (tropism testing required)

CCR5 = chemokine (C-C motif) receptor 5; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside/nucleotide reverse transcriptase inhibitor; **PI** = protease inhibitor; **RT** = reverse transcriptase.

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A 54-year-old man comes to the hospital due to 4 days of progressive nasal congestion, facial pain, swelling, and fever. The patient has taken over-the-counter decongestants, which provided no relief. He has a history of uncontrolled diabetes mellitus due to dietary and medication noncompliance. The patient's temperature is 38.3 C (101 F). Examination shows right facial swelling and purulent nasal discharge with necrotic destruction of the nasal mucosa and turbinates. The diagnosis of invasive mucormycosis is made, and surgical debridement is performed. He is started on an antifungal agent that binds to ergosterol and alters cell membrane permeability. Considering the adverse effects of this medication, which of the following should be routinely monitored in this patient?

A. Platelet count

B. Serum calcium levels

C. Serum creatine phosphokinase

D. Serum potassium and magnesium levels

E. Thyroid-stimulating hormone

Submit

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- A. Platelet count (12%)
- B. Serum calcium levels (3%)
- C. Serum creatine phosphokinase (21%)
- ✓ D. Serum potassium and magnesium levels (59%)
- E. Thyroid-stimulating hormone (3%)

Omitted
Correct answer
D

59%
Answered correctly

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Explanation

Mucormycosis should generally be treated with antifungal therapy and surgical debridement. **Amphotericin B** is the initial drug of choice. It binds **ergosterol** in fungal cell membranes to form holes. Resultant changes in membrane permeability lead to cell death. **Renal toxicity** is the most notorious side effect of amphotericin B. The drug causes renal vasoconstriction and a reduction in the glomerular filtration rate. It may also act as a direct toxin on renal epithelial cells, leading to acute tubular necrosis, renal tubular acidosis, and electrolyte disturbances. **Severe**

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Explanation

Mucormycosis should generally be treated with antifungal therapy and surgical debridement. **Amphotericin B** is the initial drug of choice. It binds **ergosterol** in fungal cell membranes to form holes. Resultant changes in membrane permeability lead to cell death. **Renal toxicity** is the most notorious side effect of amphotericin B. The drug causes renal vasoconstriction and a reduction in the glomerular filtration rate. It may also act as a direct toxin on renal epithelial cells, leading to acute tubular necrosis, renal tubular acidosis, and electrolyte disturbances. **Severe hypokalemia and hypomagnesemia** (likely reflecting increased distal tubular membrane permeability) can occur, with most patients requiring supplementation. Renal injury may also lead to decreased erythropoietin production and produce a normochromic normocytic anemia.

Patients with mucormycosis who respond to initial amphotericin therapy may be switched to posaconazole. Liver function test monitoring is recommended in patients taking azoles.

(Choice A) Examples of drugs that can cause isolated thrombocytopenia include heparin, beta-lactam antibiotics, and vancomycin.

(Choice B) Bisphosphonates (used for osteoporosis) affect bone metabolism and can cause hypocalcemia. Foscarnet (used for treating ganciclovir-resistant cytomegalovirus infections) also causes hypocalcemia.

(Choice C) Daptomycin can induce rhabdomyolysis, leading to elevated creatine phosphokinase.

(Choice E) TSH monitoring is recommended for patients taking amiodarone (used for treating arrhythmias) or lithium (used for treating bipolar disorder).

Educational objective:
Amphotericin B is a polyene antifungal drug notorious for its renal toxicity. Severe hypokalemia and hypomagnesemia are commonly seen during therapy and often require daily supplementation.

Pharmacology	Infectious Diseases	Mucormycosis
Subject	System	Topic

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A 52-year-old man is evaluated for low-grade fever, malaise, abdominal pain, and diarrhea. The patient underwent cadaveric renal transplant 6 months ago to treat renal failure from polycystic kidney disease. He takes maintenance immunosuppressive therapy. Physical examination shows mild tenderness in the lower abdominal quadrants with no rebound tenderness. Serum immunosuppressant levels are within therapeutic range, and renal function studies are normal. Colonoscopy reveals mucosal erythema and ulcerations. Biopsy shows large cells with inclusion bodies, and in situ hybridization yields viral DNA. First-line therapy for the infection is initiated. This patient is at greatest risk of which of the following from the treatment?

A. Hepatitis
B. Myopathy
C. Neutropenia
D. Pancreatitis
E. Thyroiditis

Submit

A 52-year-old man is evaluated for low-grade fever, malaise, abdominal pain, and diarrhea. The patient underwent cadaveric renal transplant 6 months ago to treat renal failure from polycystic kidney disease. He takes maintenance immunosuppressive therapy. Physical examination shows mild tenderness in the lower abdominal quadrants with no rebound tenderness. Serum immunosuppressant levels are within therapeutic range, and renal function studies are normal. Colonoscopy reveals mucosal erythema and ulcerations. Biopsy shows large cells with inclusion bodies, and in situ hybridization yields viral DNA. First-line therapy for the infection is initiated. This patient is at greatest risk of which of the following from the treatment?

A. Hepatitis (25%)
B. Myopathy (9%)
✓ C. Neutropenia (57%)
D. Pancreatitis (6%)
E. Thyroiditis (1%)

Omitted
Correct answer
C

57%
Answered correctly

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Explanation

Patients who undergo organ transplantation and are on immunosuppressive therapy are at risk for **cytomegalovirus** (CMV) **reactivation** with end-organ disease (eg, colitis, retinitis, pneumonitis). This patient has classic manifestations of **CMV colitis** including fever, fatigue, abdominal pain, and diarrhea. Because serum testing for CMV DNA may be negative, patients with suspected CMV colitis usually undergo colonoscopy with biopsy. Typical findings include colonic mucosal erythema/ulcerations. Biopsy generally reveals **large cells** with intranuclear eosinophilic

Explanation

Patients who undergo organ transplantation and are on immunosuppressive therapy are at risk for **cytomegalovirus** (CMV) **reactivation** with end-organ disease (eg, colitis, retinitis, pneumonitis). This patient has classic manifestations of **CMV colitis** including fever, fatigue, abdominal pain, and diarrhea. Because serum testing for CMV DNA may be negative, patients with suspected CMV colitis usually undergo colonoscopy with biopsy. Typical findings include colonic mucosal erythema/ulcerations. Biopsy generally reveals **large cells** with intranuclear eosinophilic inclusions and intracytoplasmic basophilic inclusions ("owls-eye" appearance).

First-line therapy for CMV colitis is intravenous **ganciclovir**. This guanine nucleoside analogue interferes with viral replication by competitively inhibiting the incorporation of guanosine triphosphate into CMV DNA strands by CMV DNA polymerase. However, this drug also impedes human DNA polymerase to a lesser degree and can interfere with host cell replication, particularly in areas of high turnover (eg, hematologic progenitor cells). Therefore, ganciclovir is often associated with prominent hematologic side effects such as **neutropenia**, anemia, and thrombocytopenia.

(Choice A) The tuberculosis medications isoniazid and pyrazinamide can cause significant hepatotoxicity.

(Choice B) Myopathy and rhabdomyolysis can be associated with the use of integrase inhibitors (eg, raltegravir, dolutegravir) in the treatment of HIV.

(Choice D) Pancreatitis is an important side effect of the HIV medication didanosine, a nucleoside reverse transcriptase inhibitor.

(Choice E) Amiodarone is an antiarrhythmic medication that can cause hypothyroidism, hyperthyroidism, or thyroiditis.

Educational objective:
First-line therapy for CMV colitis and retinitis is ganciclovir. This medication inhibits viral synthesis by blocking CMV DNA polymerase. However, ganciclovir also blocks host DNA polymerase to a lesser degree, which can lead to hematologic side effects such as neutropenia, anemia, and thrombocytopenia.

Pharmacology	Infectious Diseases	Cytomegalovirus
Subject	System	Topic

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Explanation

Patients who undergo org
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(Choice D) Pancreatitis is

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Educational objective:
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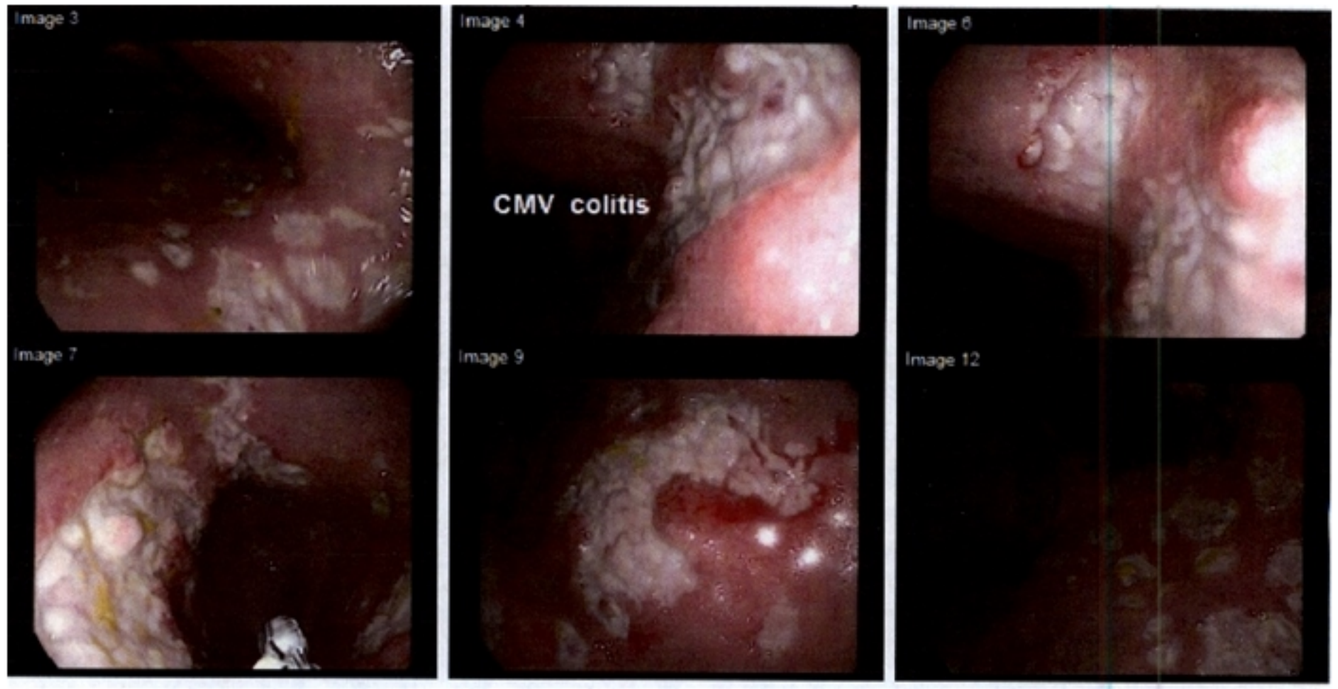

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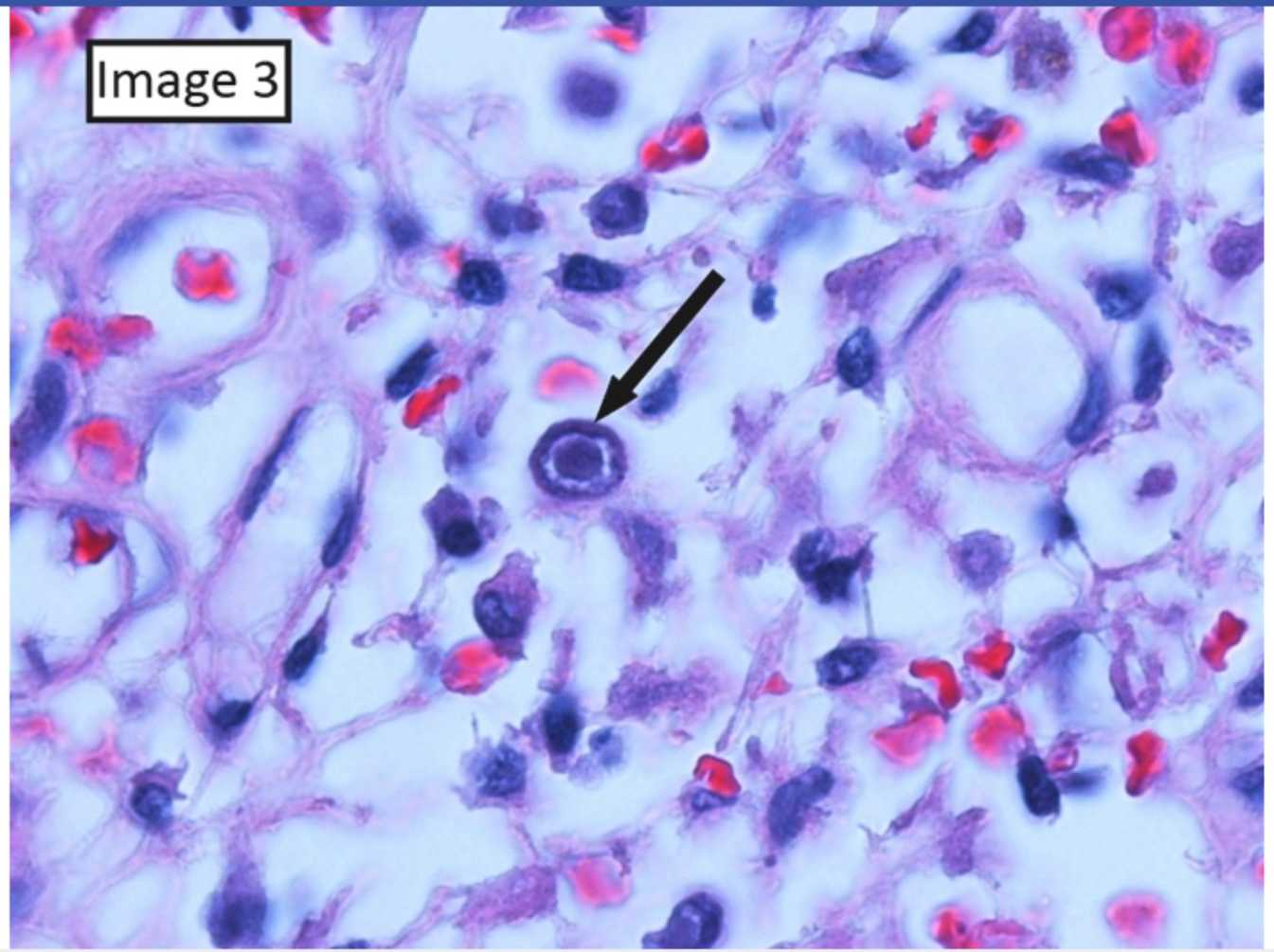

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Educational objective:
First-line therapy for CMV
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thrombocytopenia.

Pharmacology
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Drugs for treatment of tuberculosis

Drug	Mechanism of action	Side effects
(R)ifampin	Inhibition of bacterial DNA-dependent RNA polymerase	GI side effects, rash, red-orange body fluids, cytopenias
(I)soniazid	Inhibition of mycolic acid synthesis	Neurotoxicity (give vitamin B_6/pyridoxine), hepatotoxicity
(P)yrazinamide	Unclear	Hepatotoxicity, hyperuricemia
(E)thambutol	Inhibition of arabinosyl transferase (?)	Optic neuropathy

GI = gastrointestinal.

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A 43-year-old woman comes to the emergency department due to low-grade fevers and malaise. She has a history of lung transplantation due to cystic fibrosis and had 2 episodes of cytomegalovirus (CMV) viremia over the past few months, which were treated with ganciclovir. Temperature is 37.6 C (99.7 F). Physical examination is unrevealing. Chest x-ray and urinalysis are negative for infection. Polymerase chain reaction testing for CMV in blood shows elevated CMV levels consistent with CMV viremia. Given the recurrent episodes of viremia, genotype analysis is performed and demonstrates ganciclovir-resistant CMV. The patient is started on an alternate intravenous antiviral agent. She develops hypocalcemia and hypomagnesemia. Which of the following agents is the most likely cause of these side effects?

- A. Acyclovir
- B. Cidofovir
- C. Foscarnet
- D. Lamivudine
- E. Sofosbuvir
- F. Valganciclovir

Submit

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- A. Acyclovir (6%)
- B. Cidofovir (8%)
- ✓ C. Foscarnet (73%)
- D. Lamivudine (4%)
- E. Sofosbuvir (1%)
- F. Valganciclovir (5%)

Omitted
Correct answer
C

73%
Answered correctly

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Explanation

Foscarnet is a pyrophosphate analog that is sometimes used for ganciclovir-resistant cytomegalovirus (CMV) infections. Foscarnet can **chelate calcium**. Moreover, foscarnet-induced renal wasting of magnesium may lead to **hypomagnesemia** and a reduction in the release of parathyroid hormone, which contributes to the hypocalcemic state. Both hypocalcemia and hypomagnesemia can promote **seizures**.

C

Explanation

Foscarnet is a pyrophosphate analog that is sometimes used for ganciclovir-resistant cytomegalovirus (CMV) infections. Foscarnet can **chelate calcium**. Moreover, foscarnet-induced renal wasting of magnesium may lead to **hypomagnesemia** and a reduction in the release of parathyroid hormone, which contributes to the hypocalcemic state. Both hypocalcemia and hypomagnesemia can promote **seizures**.

(Choice A) Major toxicities of acyclovir (used in some herpes simplex virus infections) include crystal nephropathy and neurotoxicity that manifests as delirium and/or tremor.

(Choice B) Cidofovir, used in some cases of CMV retinitis, is associated with nephrotoxicity manifesting as proteinuria or elevated creatinine.

(Choice D) Lamivudine is a nucleoside reverse transcriptase inhibitor (NRTI). Side effects are unusual with lamivudine, unlike other NRTIs. Lamivudine is occasionally associated with peripheral neuropathy and lactic acidosis.

(Choice E) Sofosbuvir inhibits nonstructural protein 5B (NS5B), an RNA-dependent RNA polymerase needed for hepatitis C virus replication. Adverse effects associated with its use include fatigue and nausea.

(Choice F) Valganciclovir is a ganciclovir prodrug and is unlikely to be useful against ganciclovir-resistant CMV. Ganciclovir is associated with severe neutropenia, which can be exacerbated by other bone-marrow suppressing agents (eg, zidovudine, trimethoprim-sulfamethoxazole).

Educational objective:
Foscarnet is an analog of pyrophosphate that can chelate calcium and promote nephrotoxic renal magnesium wasting. These toxicities can result in hypocalcemia and hypomagnesemia, which can cause seizures.

Pharmacology	Infectious Diseases	Foscarnet
Subject	System	Topic

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A 47-year-old man comes to the emergency department due to fever and fatigue. He has a history of HIV and has not been taking his antiretrovirals consistently. His temperature is 38.3 C (100.9 F), blood pressure is 110/70 mm Hg, pulse is 104/min, and respirations are 20/min. Physical examination is notable for hepatosplenomegaly and multiple erythematous papules. Laboratory studies show pancytopenia. *Histoplasma* antigen testing is positive. Intravenous amphotericin B therapy is initiated for disseminated histoplasmosis. A day later, the patient develops palpitations and weakness. An ECG reveals frequent premature ventricular beats. If these new signs and symptoms are caused by drug toxicity, they are most likely related to which of the following?

A. Bone marrow suppression
B. Cardiac muscle cell damage
C. Hepatocyte necrosis
D. Pulmonary hypertension
E. Renal tubular dysfunction

Submit

A 47-year-old man comes to the emergency department due to fever and fatigue. He has a history of HIV and has not been taking his antiretrovirals consistently. His temperature is 38.3 C (100.9 F), blood pressure is 110/70 mm Hg, pulse is 104/min, and respirations are 20/min. Physical examination is notable for hepatosplenomegaly and multiple erythematous papules. Laboratory studies show pancytopenia. *Histoplasma* antigen testing is positive. Intravenous amphotericin B therapy is initiated for disseminated histoplasmosis. A day later, the patient develops palpitations and weakness. An ECG reveals frequent premature ventricular beats. If these new signs and symptoms are caused by drug toxicity, they are most likely related to which of the following?

A. Bone marrow suppression (3%)

B. Cardiac muscle cell damage (19%)

C. Hepatocyte necrosis (5%)

D. Pulmonary hypertension (2%)

✓ E. Renal tubular dysfunction (70%)

Omitted
Correct answer
E

70%
Answered correctly

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Explanation

This patient with HIV has fever, fatigue, hepatosplenomegaly, skin lesions, and pancytopenia; these are consistent with disseminated histoplasmosis, as evidenced by the positive *Histoplasma* antigen test. **Amphotericin B** is the drug of choice to treat many systemic mycoses. It is also the most toxic antifungal medication.

The most dangerous adverse effect of amphotericin B is its **nephrotoxicity**; this is due to both a decrease in glomerular filtration rate and direct

Explanation

This patient with HIV has fever, fatigue, hepatosplenomegaly, skin lesions, and pancytopenia; these are consistent with disseminated histoplasmosis, as evidenced by the positive *Histoplasma* antigen test. **Amphotericin B** is the drug of choice to treat many systemic mycoses. It is also the most toxic antifungal medication.

The most dangerous adverse effect of amphotericin B is its **nephrotoxicity**; this is due to both a decrease in glomerular filtration rate and direct toxic effects on the tubular epithelium. Nephrotoxicity can lead to anemia (decreased erythropoietin production) and electrolyte abnormalities. **Hypokalemia** and (less often) hypomagnesemia are common due to an increase in the membrane permeability of the distal tubule. Hypokalemia can cause **weakness** and **arrhythmias**. ECG findings in hypokalemia include T wave flattening, ST-segment depression, prominent U waves, and premature atrial and ventricular contractions. Profound hypokalemia can cause ventricular tachycardia or fibrillation.

(Choice A) Bone marrow suppression is associated with many chemotherapeutic agents, chloramphenicol, zidovudine, and gold-containing medications. Bone marrow suppression would not cause ECG changes.

(Choice B) Doxorubicin and daunorubicin are associated with irreversible dose-dependent cardiotoxicity, which is not a side effect of amphotericin B.

(Choice C) Acetaminophen and halothane are examples of medications that can cause liver necrosis. Amphotericin B can lead to liver toxicity, not necrosis. Arrhythmias and palpitations are more likely caused by electrolyte abnormalities due to renal tubular dysfunction.

(Choice D) Busulfan and bleomycin are examples of drugs that cause pulmonary fibrosis and can lead to pulmonary hypertension.

Educational objective:
Hypokalemia and hypomagnesemia are common electrolyte disturbances in patients undergoing treatment with amphotericin B and reflect an increase in distal tubular membrane permeability.

Pharmacology	Infectious Diseases	Adverse drug reaction
Subject	System	Topic

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A 43-year-old man comes to the office after a recent hospitalization for *Pneumocystis* pneumonia. The patient is taking trimethoprim-sulfamethoxazole and says that his pulmonary symptoms are better. He has a history of HIV and was on highly active antiretroviral therapy until self-discontinuing treatment 2 years ago. On physical examination, the patient appears to be in no acute distress. BMI is 20 kg/m^2. A few crackles are heard at the lung bases. His most recent CD4 count is 122/mm^3. After discussing medical compliance and the need to resume antiretroviral therapy, HIV genotyping assay is performed. Additional testing for HLA-B*57:01 yields positive results. Which of the following medications is contraindicated in this patient due to the risk of a potentially fatal hypersensitivity reaction?

A. Abacavir
B. Darunavir
C. Efavirenz
D. Emtricitabine
E. Nevirapine

Submit

A 43-year-old man comes to the office after a recent hospitalization for *Pneumocystis* pneumonia. The patient is taking trimethoprim-sulfamethoxazole and says that his pulmonary symptoms are better. He has a history of HIV and was on highly active antiretroviral therapy until self-discontinuing treatment 2 years ago. On physical examination, the patient appears to be in no acute distress. BMI is 20 kg/m^2. A few crackles are heard at the lung bases. His most recent CD4 count is 122/mm^3. After discussing medical compliance and the need to resume antiretroviral therapy, HIV genotyping assay is performed. Additional testing for HLA-B*57:01 yields positive results. Which of the following medications is contraindicated in this patient due to the risk of a potentially fatal hypersensitivity reaction?

- ✓ A. Abacavir (52%)
- B. Darunavir (6%)
- C. Efavirenz (18%)
- D. Emtricitabine (12%)
- E. Nevirapine (9%)

Omitted
Correct answer
A

52%
Answered correctly

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Explanation

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) used in the treatment of HIV/AIDS. Allergic responses can occur with many HIV/AIDS medications. **Abacavir hypersensitivity reaction** (AHR) is an allergic reaction that develops in 2%–8% of patients and is strongly associated with the HLA-B*57:01 allele of the human leukocyte antigen (HLA) system. AHR occurs due to direct binding of abacavir to a segment on the **HLA-B*57:01** molecule, which alters the presentation of self-peptides to the immune system and results in a **delayed hypersensitivity**

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(Choice B) Common side effects of protease inhibitors such as darunavir include metabolic abnormalities (hyperglycemia), gastrointestinal symptoms, and lipodystrophy.

(Choices C and E) The non-NRTIs efavirenz and nevirapine may cause Stevens-Johnson syndrome and toxic epidermal necrolysis, but these conditions are not associated with HLA alleles. Liver function abnormalities can also occur with these 2 non-NRTIs.

(Choice D) Emtricitabine, another NRTI, has been associated with an asymptomatic macular rash on the palms or soles; no genetic basis for this reaction has been identified.

Educational objective:
Abacavir hypersensitivity reaction occurs in 2%–8% of patients and is strongly associated with the HLA-B*57:01 allele.

References

- Abacavir pharmacogenetics—from initial reports to standard of care.
- Hypersensitivity reactions to HIV therapy.

Pharmacology	Infectious Diseases	Antiretroviral therapy
Subject	System	Topic

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Explanation

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HIV/AIDS medications. A
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Educational objective:
Abacavir hypersensitivity

References

- Abacavir pharmacoge
- Hypersensitivity reacti

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A 56-year-old man with advanced AIDS comes to the emergency department due to several weeks of progressive fever, night sweats, weight loss, diarrhea, and generalized weakness. Physical examination shows mucosal pallor, generalized lymphadenopathy, and hepatosplenomegaly. Laboratory studies reveal anemia and elevated alkaline phosphatase and lactate dehydrogenase levels. CD4 count is 16/mm^3. Bone marrow biopsy shows aggregates of epithelioid histiocytes with foamy cytoplasm and numerous acid-fast intracellular organisms. Nucleic acid amplification test of the sample for *Mycobacterium tuberculosis* is negative. Which of the following pathogens is the most likely cause of this patient's illness?

A. *Cryptococcus neoformans*
B. *Cryptosporidium parvum*
C. *Legionella pneumophila*
D. *Mycobacterium avium*
E. *Mycobacterium marinum*
F. *Nocardia asteroides*

Submit

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- A. *Cryptococcus neoformans* (5%)
- B. *Cryptosporidium parvum* (14%)
- C. *Legionella pneumophila* (1%)
- ✓ D. *Mycobacterium avium* (61%)
- E. *Mycobacterium marinum* (1%)
- F. *Nocardia asteroides* (15%)

Omitted
Correct answer
D

61%
Answered correctly

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04/15/2020
Last Updated

Explanation

This patient's subacute systemic symptoms (eg, fever, night sweats, weight loss, weakness), lymphadenopathy, hepatosplenomegaly, elevated alkaline phosphatase, and intracellular acid-fast bacteria raise strong suspicion for disseminated ***Mycobacterium avium* complex (MAC)**. MAC is an infection caused by the **nontuberculous** mycobacteria *M avium* and *Mycobacterium intracellulare*. Although these infections can occur in

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MAC organisms are acquired by ingestion or inhalation. They are phagocytosed by macrophages but initially evade destruction due to microbial virulence factors that prevent phagolysosome formation. In healthy individuals, the infection is controlled with the cell-mediated immune response. However, in patients with **advanced AIDS**, the body is unable to generate sufficient CD4-mediated cytokines (eg, interferon-gamma) to activate macrophages, which allows the pathogen to spread through the bloodstream and reticuloendothelial system.

Most patients with disseminated infection have **nonspecific symptoms** (eg, fever, weight loss, diarrhea). Widespread involvement of the reticuloendothelial system often causes anemia, hepatosplenomegaly, and/or elevated alkaline phosphatase and lactate dehydrogenase. The diagnosis is usually made with blood cultures, but results may take weeks because mycobacteria grow slowly. Bone marrow biopsy with histopathology typically shows evidence of granulomata composed of foamy epithelioid cells and multinucleated Langhans cells (similar to *Mycobacterium tuberculosis* infection). **Intracellular, acid-fast bacilli** are usually present.

(Choice A) *Cryptococcus neoformans*, an encapsulated yeast, is a common cause of meningoencephalitis in patients with advanced AIDS. Although it is a facultative intracellular pathogen, it does not stain with acid-fast preparations. The pathogen is usually visualized with India ink, mucicarmine, or methenamine stains.

(Choice B) *Cryptosporidium parvum* is a common cause of high-volume diarrhea and biliary disease in patients with advanced AIDS. This organism's oocytes can be visualized with modified acid-fast stain, and the pathogen is intracellular. However, it infects epithelial cells and does not spread through the reticuloendothelial system to the bone marrow or lymph nodes.

(Choice C) *Legionella pneumophila* is a gram-negative, intracellular bacteria that often causes gastrointestinal symptoms prior to pneumonia. However, it does not stain with acid-fast and does not generally cause lymphadenopathy or bone marrow infection.

(Choice E) *Mycobacterium marinum* is a nontuberculous mycobacterium that can cause skin and soft tissue infection following exposure to water (eg, fish tanks). It does not generally cause several weeks of diarrhea, lymphadenopathy, and hepatosplenomegaly.

(Choice F) *Nocardia asteroides*, a partially acid-fast organism, typically causes pneumonia and/or brain abscess. Gastrointestinal symptoms,

diagnosis is usually made with blood cultures, but results may take weeks because mycobacteria grow slowly. Bone marrow biopsy with histopathology typically shows evidence of granulomata composed of foamy epithelioid cells and multinucleated Langhans cells (similar to *Mycobacterium tuberculosis* infection). **Intracellular, acid-fast bacilli** are usually present.

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(Choice F) *Nocardia asteroides*, a partially acid-fast organism, typically causes pneumonia and/or brain abscess. Gastrointestinal symptoms, lymphadenopathy, and bone marrow involvement would be atypical.

Educational objective:
Mycobacterium avium complex (MAC) infections are common in patients with advanced AIDS. The bacterium often spreads through the bloodstream and reticuloendothelial system and causes nonspecific symptoms (eg, fever, fatigue, weight loss, diarrhea), lymphadenopathy, and hepatosplenomegaly. Diagnosis is often made on blood culture or bone marrow aspirate (intracellular acid-fast bacteria that are not *Mycobacterium tuberculosis*).

Pharmacology	Infectious Diseases	Nontuberculous mycobacterial diseases
Subject	System	Topic

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alkaline phosphatase, and intracellular acid-fast bacteria raise strong suspicion for disseminated ***Mycobacterium avium* complex (MAC)**. MAC

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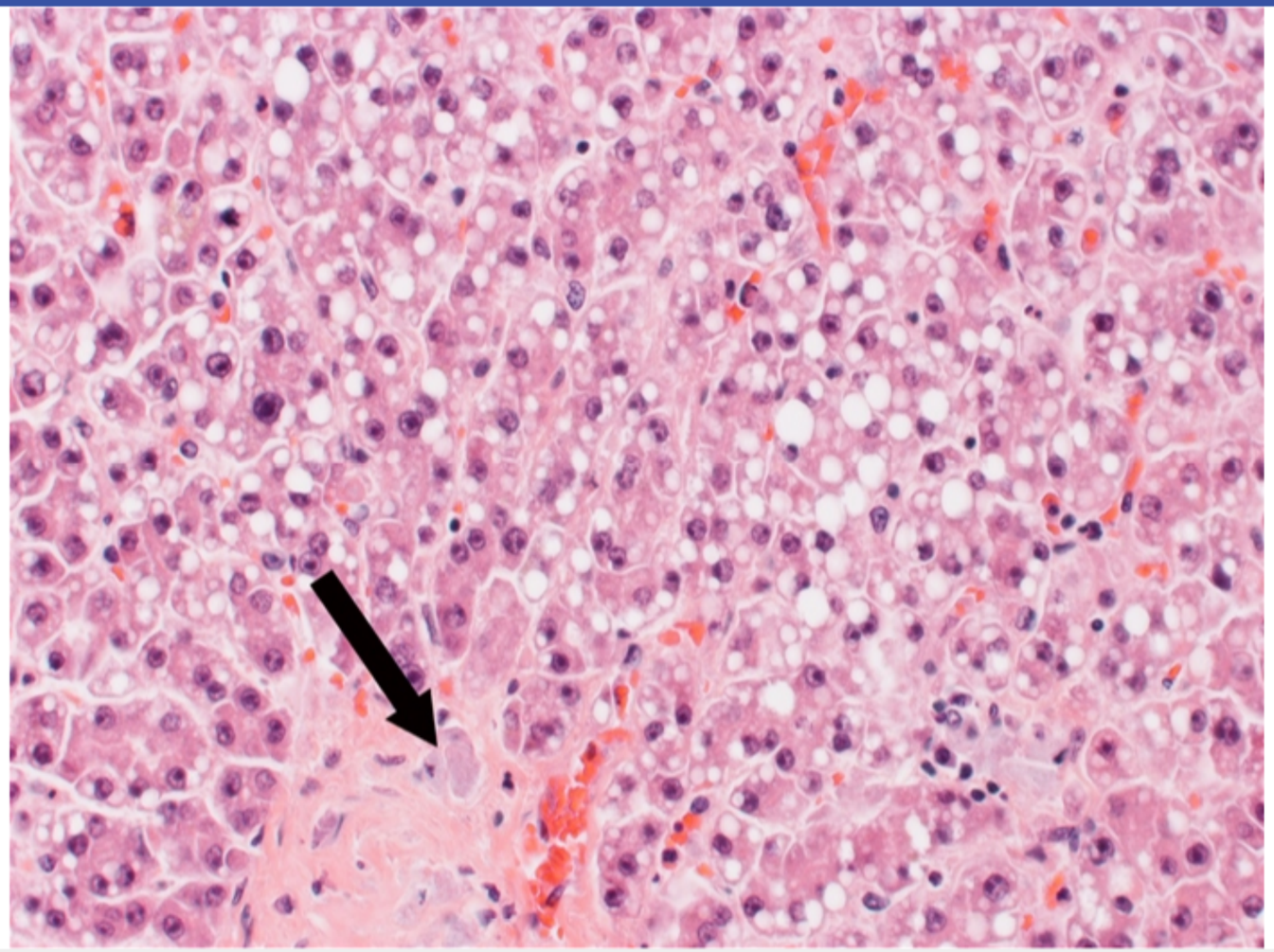

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Mycobacterium avium complex (MAC) infections are common in patients with advanced AIDS. The bacterium often spreads through the bloodstream and reticuloendothelial system and causes nonspecific symptoms (eg, fever, fatigue, weight loss, diarrhea), lymphadenopathy, and hepatosplenomegaly. Diagnosis is often made on blood culture or bone marrow aspirate (intracellular acid-fast bacteria that are not *Mycobacterium tuberculosis*).

Pharmacology	Infectious Diseases	Nontuberculous mycobacterial diseases
Subject	System	Topic

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A 23-year-old man is hospitalized for fever, headache, and confusion. He does not use tobacco or illicit drugs and is monogamous with his wife. The patient's cerebrospinal fluid analysis reveals lymphocytic pleocytosis, and a PCR is positive for herpesvirus. The patient is treated with intravenous high-dose acyclovir. Fever and mental status gradually improve, but on the third day of hospitalization the patient's serum creatinine level increases to 3.4 mg/dL from a baseline of 0.9 mg/dL at admission. The observed finding could have been prevented by which of the following?

A. Aggressive intravenous hydration
B. Careful taking of allergy history
C. Monitoring of blood drug levels
D. Pretreatment with allopurinol
E. Pretreatment with prednisone

Submit

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- ✓ A. Aggressive intravenous hydration (67%)
- B. Careful taking of allergy history (3%)
- C. Monitoring of blood drug levels (16%)
- D. Pretreatment with allopurinol (7%)
- E. Pretreatment with prednisone (5%)

Omitted
Correct answer
A

67%
Answered correctly

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Last Updated

Explanation

The acute elevation of this patient's serum creatinine on the third day of hospitalization is likely due to **acyclovir nephrotoxicity**, which occurs in 5%-10% of patients who receive the drug intravenously. Acyclovir is excreted principally in the urine via glomerular filtration and tubular secretion. When the acyclovir concentration in the collecting duct exceeds its solubility, crystallization, crystalluria, and renal tubular damage can occur. In most cases, this toxic complication is transient and can be prevented (as well as treated) with **adequate hydration** and a reduction in the rate of drug infusion.

Explanation

The acute elevation of this patient's serum creatinine on the third day of hospitalization is likely due to **acyclovir nephrotoxicity**, which occurs in 5%-10% of patients who receive the drug intravenously. Acyclovir is excreted principally in the urine via glomerular filtration and tubular secretion. When the acyclovir concentration in the collecting duct exceeds its solubility, crystallization, crystalluria, and renal tubular damage can occur. In most cases, this toxic complication is transient and can be prevented (as well as treated) with **adequate hydration** and a reduction in the rate of drug infusion.

(Choice B) Acute interstitial nephritis (AIN) is an allergic inflammation of the kidney that is most commonly triggered by medications and is often associated with fever, rash, and eosinophilia. However, acyclovir is not a common cause of AIN; common causes include nonsteroidal anti-inflammatory drugs, penicillins, cephalosporins, diuretics, and allopurinol.

(Choice C) Monitoring of acyclovir blood levels is not always effective in preventing nephrotoxicity. During states of low intravascular volume (eg, dehydration), nephrotoxicity can develop secondary to increased urinary concentration even when acyclovir blood levels are not within the established toxic range.

(Choice D) Allopurinol blocks xanthine oxidase, which reduces the formation of uric acid. Pretreatment with allopurinol is often used in patients with lymphoma and leukemia to prevent urate crystal nephropathy due to tumor lysis syndrome. Acyclovir nephrotoxicity is mediated by the formation of acyclovir crystals, not urate crystals, so allopurinol pretreatment would be ineffective.

(Choice E) Pretreatment with prednisone can help prevent radiocontrast-induced allergic reactions. Prednisone does not prevent the formation of acyclovir crystals.

Educational objective:
Intravenous acyclovir can cause crystalline nephropathy if adequate hydration is not also provided.

Pharmacology	Infectious Diseases	Acyclovir
Subject	System	Topic

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A 13-year-old boy is brought to the clinic by his parents due to a change in behavior. His special education teacher reported that for the last several weeks he has frequently taken off his shoes to scratch his feet during class. The patient has a history of learning disability but is otherwise healthy. Examination shows erythema and excoriations between the toes of both feet. Microscopy of skin scrapings from the rash is shown in the exhibit. Which of the following antimicrobial drugs is likely to be most effective against the pathogen causing this patient's condition?

- A. Albendazole
- B. Clotrimazole
- C. Mupirocin
- D. Nystatin
- E. Permethrin

Submit

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A. Albendazole (12%)
✓ B. Clotrimazole (56%)
C. Mupirocin (3%)
D. Nystatin (14%)
E. Permethrin (12%)

Omitted
Correct answer
B

56%
Answered correctly

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Explanation

Tinea pedis	
Etiology	• *Trichophyton* species (most common)
Clinical features	• Pruritus, erythema, erosions/scaling • Most often interdigital or covering the sole (moccasin type)

Explanation

Tinea pedis	
Etiology	• *Trichophyton* species (most common)
Clinical features	• Pruritus, erythema, erosions/scaling • Most often interdigital or covering the sole (moccasin type) • Segmented hyphae on KOH preparation
Treatment	• Topical antifungal therapy (eg, azoles, terbinafine) • Keep feet dry & dispose of old footwear

This patient has a pruritic, erythematous rash of the feet. Potassium hydroxide microscopy of skin scrapings shows branching hyphae, confirming the diagnosis of **tinea pedis** (athlete's foot). Tinea pedis is a superficial infection of the epidermis caused by **dermatophytes**, especially *Trichophyton rubrum* and similar species. The organisms are widespread and are often acquired following exposure to public places while barefoot (eg, athletic facilities, swimming pools). They can also spread from other areas (eg, groin [tinea cruris], body [tinea corporis]) on the same patient via autoinoculation.

Tinea pedis most commonly occurs between the toes (interdigital pattern) but in chronic cases can cause a hyperkeratotic rash extending up the sides of the feet (moccasin pattern). Tinea pedis is treated with a variety of **topical antifungals**, including azoles (eg, miconazole, **clotrimazole**), allylamines (eg, terbinafine), and tolnaftate. However, nystatin (primarily used for *Candida* infections) is not effective against dermatophytes **(Choice D)**.

(Choice A) Albendazole is an antihelminthic agent used to treat cutaneous larva migrans, which presents with pruritic, red/brown serpiginous tracks in the skin. The feet are typically the initial location of infection, but symptoms would not be confined to the interdigital skin.

(Choice C) Topical mupirocin is used to treat impetigo, which presents with well-defined erythematous, erosive lesions with yellow crust.

Treatment	terbinafine) • Keep feet dry & dispose of old footwear

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(Choice E) Permethrin is used for scabies, which can affect the interdigital skin but presents with small papules, pustules, and burrows. Microscopy of skin scrapings shows mites or ova and fecal matter.

Educational objective:
Tinea pedis is a superficial infection of the epidermis caused by dermatophytes (eg, *Trichophyton rubrum*). It most often presents as a pruritic, erythematous rash between the toes that frequently extends along the sole. Potassium hydroxide microscopy of skin scrapings shows branching hyphae. Treatment options include a variety of topical antifungals (eg, clotrimazole), but not nystatin.

Pharmacology	Infectious Diseases	Tinea
Subject	System	Topic

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Treatment

terbinafine)

- Keep foot dry & dispose of old footwear

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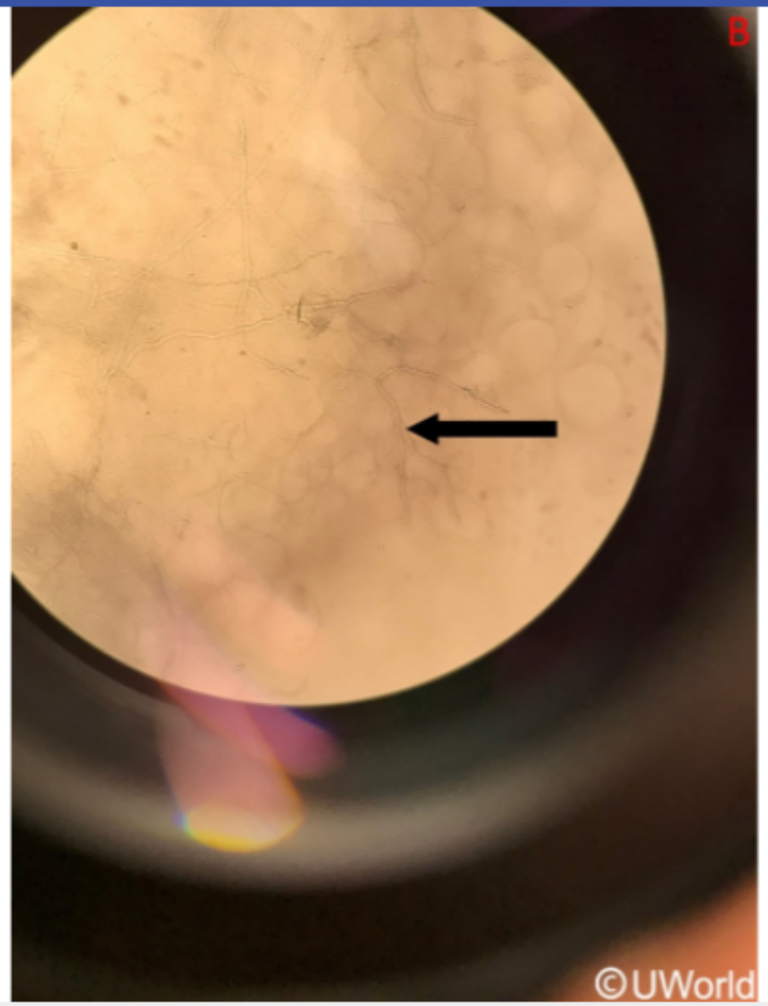

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Treatment	terbinafine) • Keep feet dry & dispose of old footwear

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Pharmacology	Infectious Diseases	Tinea
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Treatment	terbinafine) • Keep feet dry & dispose of old footwear

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Pharmacology
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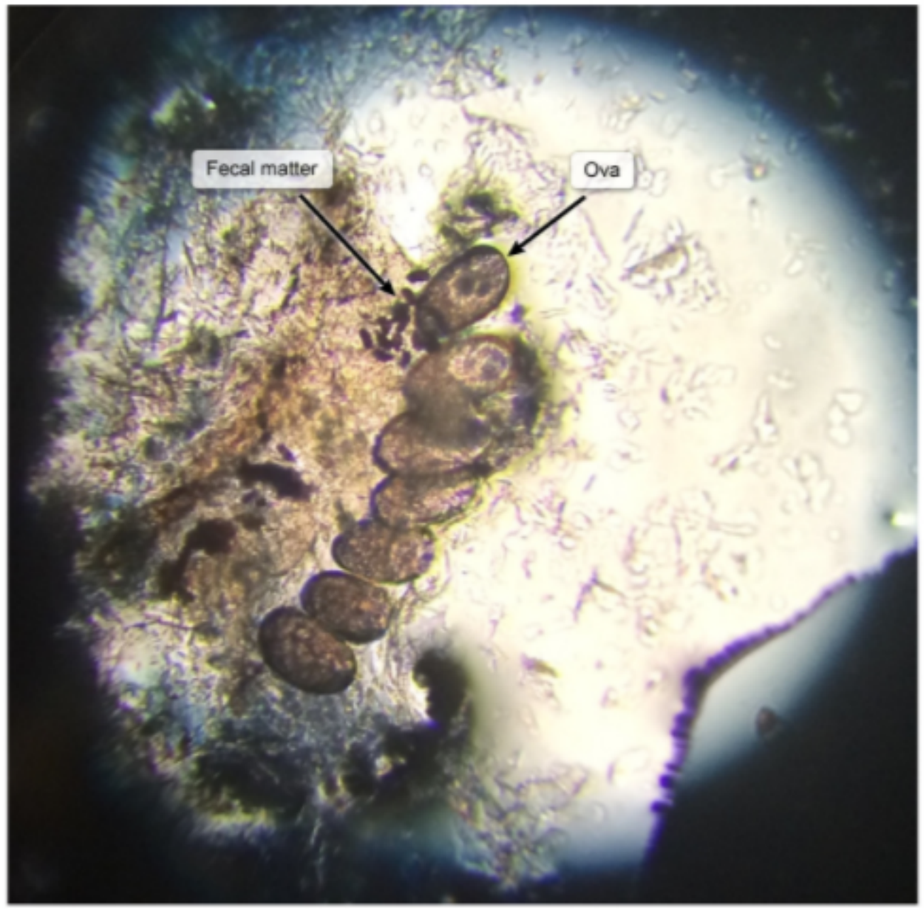
Treatment
- terbinafine)
- Keep feet dry & dispose of old footwear

Exhibit Display

Scabies



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Treatment

terbinafine)

- Keep feet dry & dispose of old footwear

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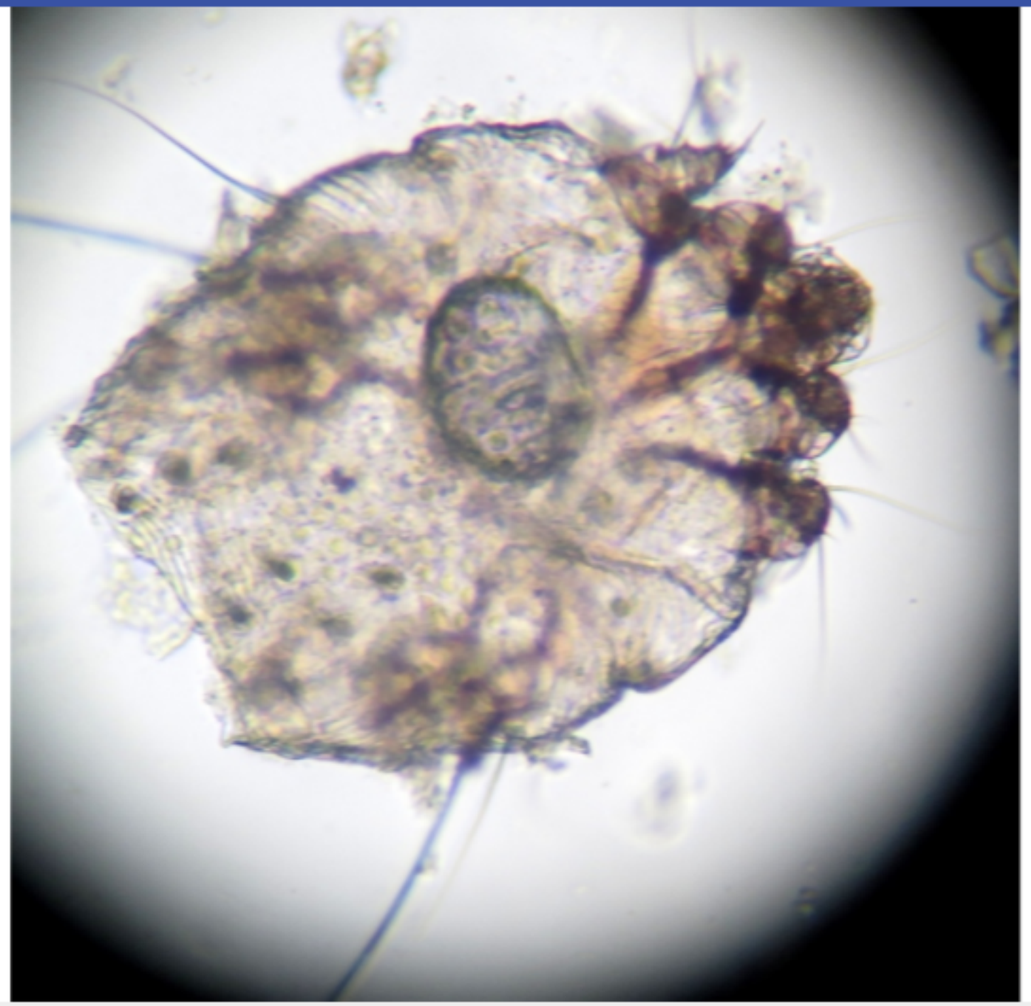

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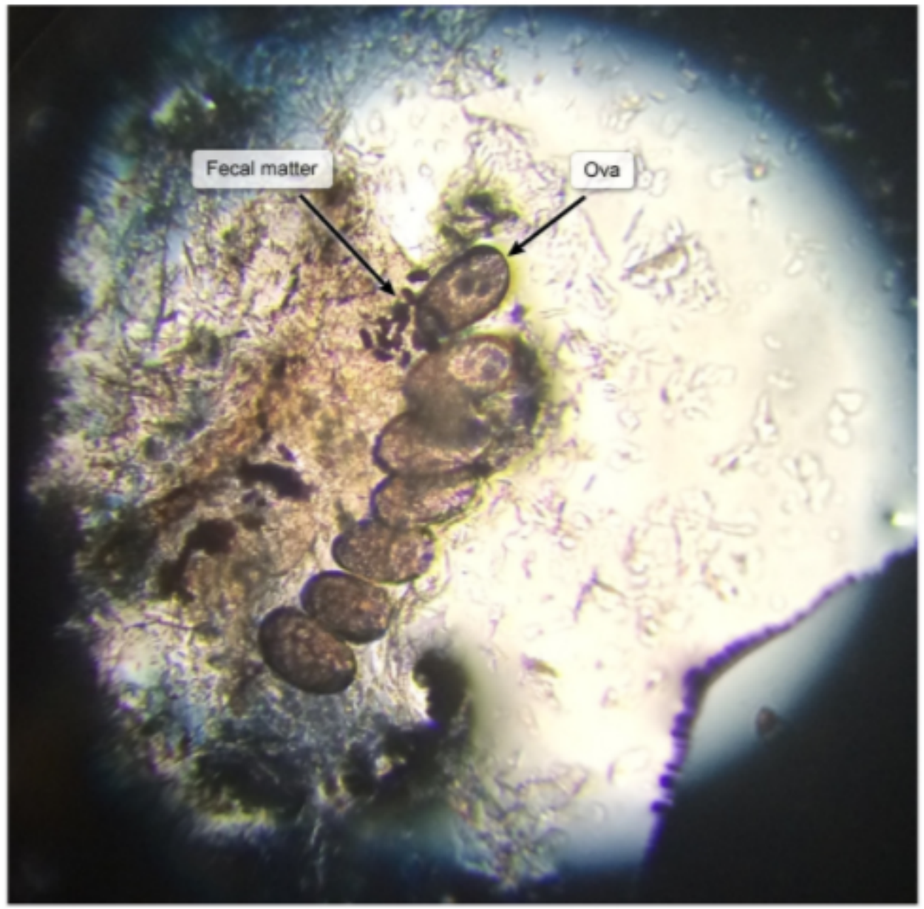
Treatment

- Keep feet dry & dispose of old footwear

Exhibit Display

Scabies



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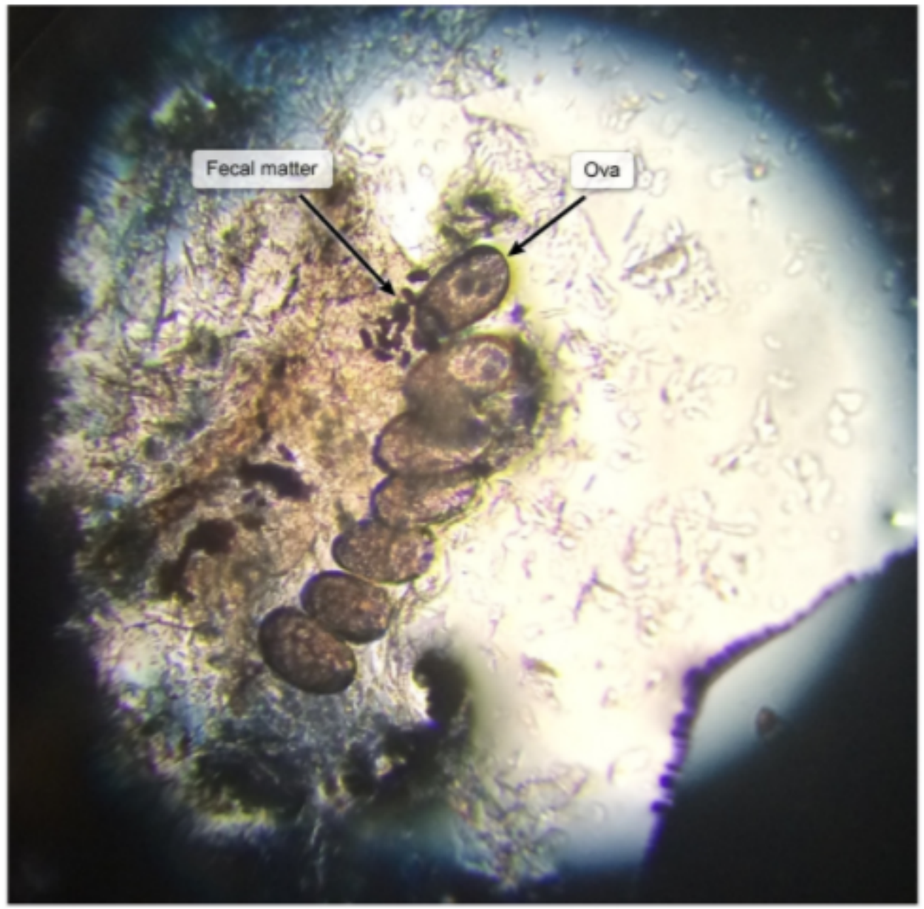
Treatment

- Keep feet dry & dispose of old footwear

Exhibit Display

Scabies



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Gram-positive bacteria are injected under the skin of experimental animals. Three days later, the animals are treated with antibiotic therapy. Aspirates taken from the infection site are plated on nutrient-rich agar. The isolated bacteria assume a spherical configuration when placed in an isotonic solution and disintegrate rapidly when placed in a hypotonic solution. Which of the following antibiotics was most likely administered to the animals in this experiment?

A. Azithromycin
B. Cefuroxime
C. Chloramphenicol
D. Ciprofloxacin
E. Doxycycline

Submit

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- A. Azithromycin (9%)
- ✓ B. Cefuroxime (60%)
- C. Chloramphenicol (11%)
- D. Ciprofloxacin (8%)
- E. Doxycycline (9%)

Omitted
Correct answer
B

60%
Answered correctly

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03/12/2020
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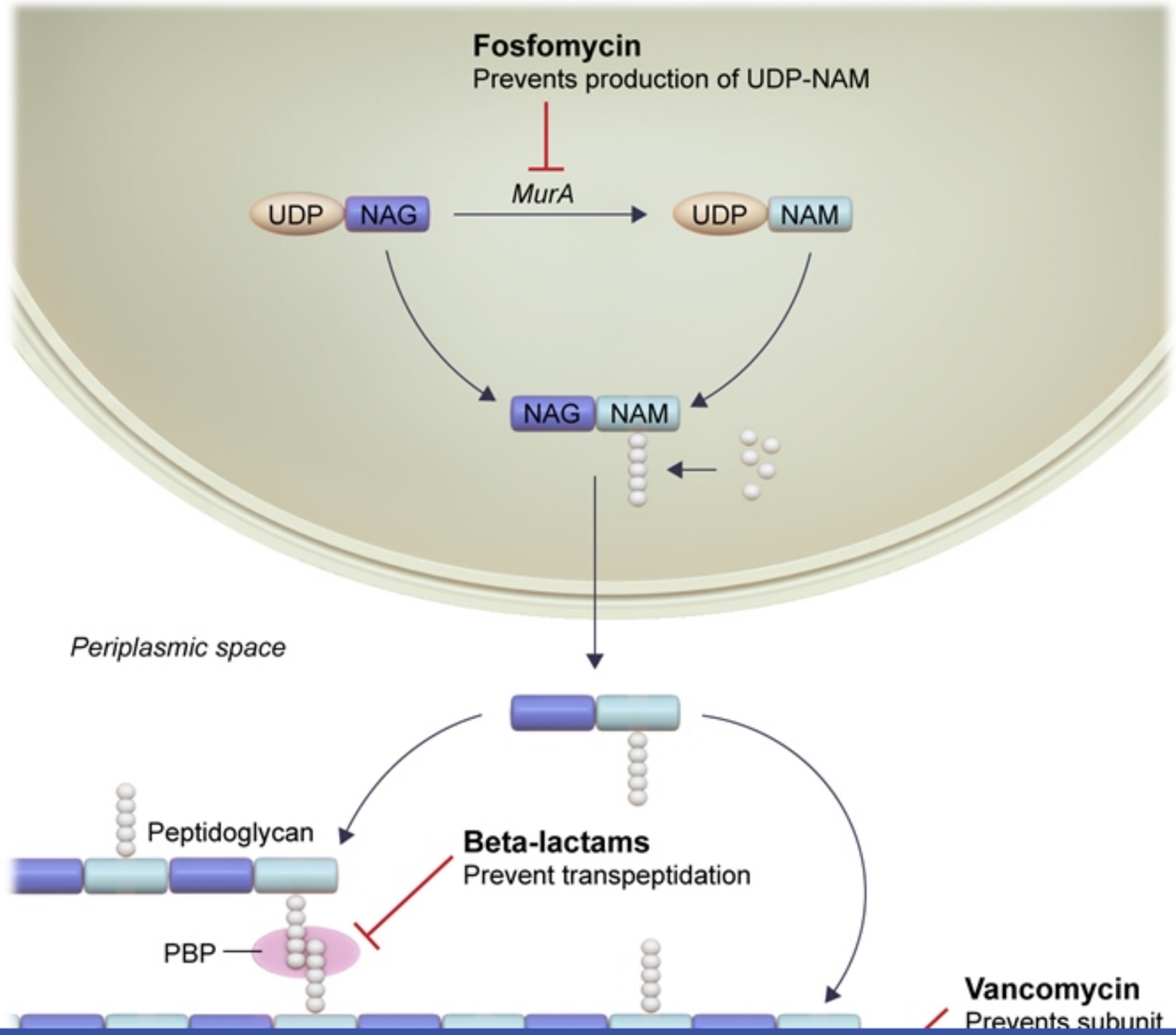
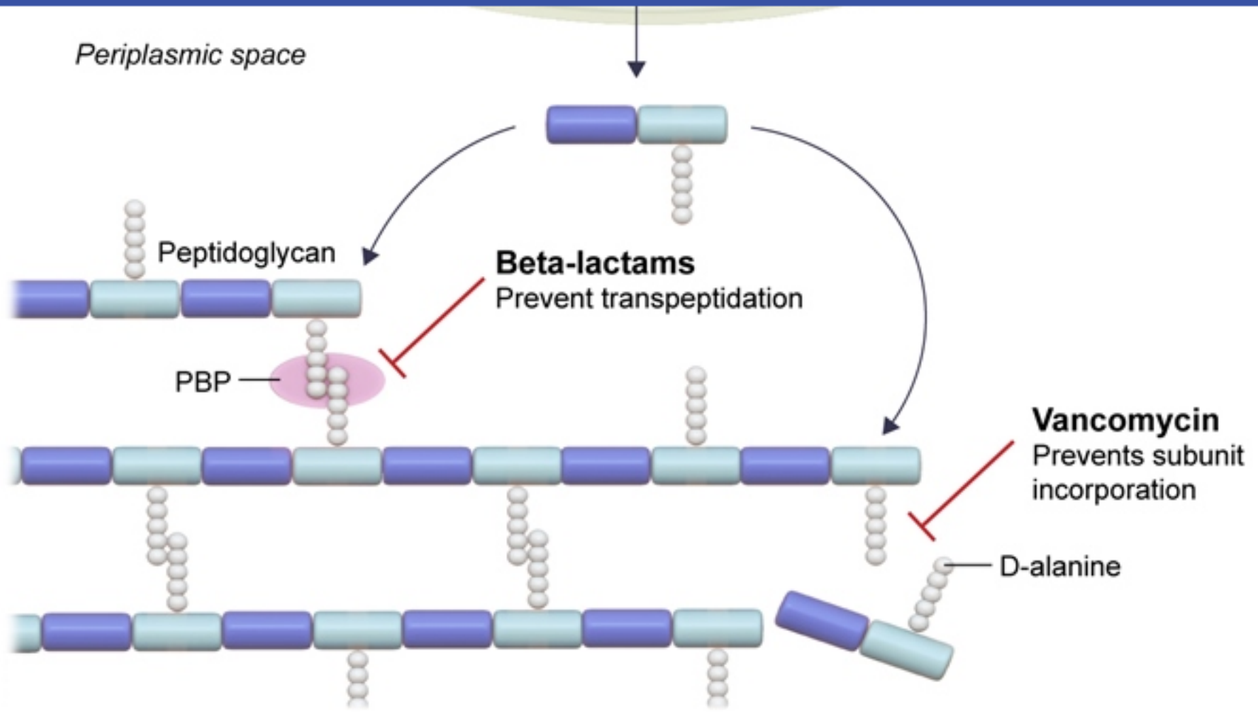
Explanation

Antibiotics that inhibit cell wall synthesis

Fosfomycin
Prevents production of UDP-NAM

Antibiotics that inhibit cell wall synthesis





NAG = N-acetylglucosamine; **NAM** = N-acetylmuramic acid; **PBP** = penicillin-binding protein; **UDP** = uridine diphosphate.
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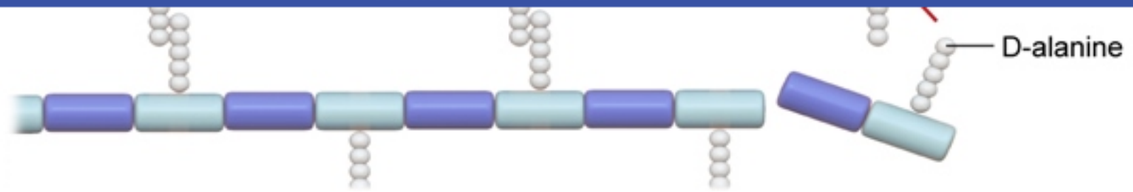
The **bacterial cell wall** is composed of **rigid**, cross-linked peptidoglycan pentads on a glucosamine backbone. Its primary purpose is to provide **external structure** to the bacterium and **prevent disfigurement** or lysis in changing osmotic gradients. In this experiment, the assumption of a spherical shape in an isotonic solution and lysis in a hypotonic solution indicate **disruption** of the bacterial cell wall. Several classes of antibiotics target cell wall synthesis, including fosfomycin, vancomycin, penicillins, and **cephalosporins** (eg, **cefuroxime**).

(Choices A and C) Azithromycin and chloramphenicol inhibit the bacterial 50S ribosomal subunit. They have no effect on the cell wall and would not alter bacterial shape in different osmotic gradients. Side effects of chloramphenicol include dose-related myelosuppression and aplastic anemia.

(Choice D) Fluoroquinolones (eg, ciprofloxacin) inhibit bacterial DNA topoisomerase and gyrase, which results in bacterial cell death due to DNA damage. They do not affect the cell wall.



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(Choice E) Doxycycline disrupts bacterial protein synthesis by inhibiting the bacterial 30S ribosomal subunit. It has no effect on the rigidity of the cell wall.

Educational objective:
The bacterial cell wall protects the organism from osmotic stress. Antibiotics that target the cell wall result in bacterial lysis in hypotonic solutions. Fosfomycin, vancomycin, penicillins, and cephalosporins all disrupt bacterial cell wall synthesis.

Pharmacology	Infectious Diseases	Cephalosporins
Subject	System	Topic

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A 32-year-old man with HIV is diagnosed with pulmonary tuberculosis and started on a 4-drug combination therapy. On a follow-up visit 3 weeks later, he reports red urine and red staining of his contact lenses. A drug susceptibility test of his sputum isolates of *Mycobacterium tuberculosis* shows resistance to several antimycobacterial agents. Which of the following best explains the bacterial resistance to the drug responsible for this patient's current symptoms?

A. Altered structure of enzymes involved in bacterial DNA winding-unwinding

B. Altered structure of enzymes involved in bacterial RNA synthesis

C. Altered structure of bacterial ribosomal proteins

D. Decreased activity of bacterial catalase-peroxidase

E. Upregulation of bacterial beta-lactamase synthesis

Submit

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- A. Altered structure of enzymes involved in bacterial DNA winding-unwinding (5%)
- ✓ B. Altered structure of enzymes involved in bacterial RNA synthesis (70%)
- C. Altered structure of bacterial ribosomal proteins (15%)
- D. Decreased activity of bacterial catalase-peroxidase (7%)
- E. Upregulation of bacterial beta-lactamase synthesis (1%)

Omitted
Correct answer
B

70%
Answered correctly

04 secs
Time Spent

01/28/2020
Last Updated

Explanation

Drugs for treatment of tuberculosis		
Drug	**Mechanism of action**	**Side effects**
(R)ifampin	Inhibition of bacterial DNA-dependent RNA polymerase	GI side effects, rash, red-orange body fluids, cytopenias

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(R)ifampin	Inhibition of bacterial DNA-dependent RNA polymerase	GI side effects, rash, red-orange body fluids, cytopenias
(I)soniazid	Inhibition of mycolic acid synthesis	Neurotoxicity (give vitamin B_6/pyridoxine), hepatotoxicity
(P)yrazinamide	Unclear	Hepatotoxicity, hyperuricemia
(E)thambutol	Inhibition of arabinosyl transferase (?)	Optic neuropathy

GI = gastrointestinal.

This patient with HIV has active **pulmonary tuberculosis**, typically treated with a 4-drug combination of a rifamycin (eg, rifampin, rifabutin), isoniazid, pyrazinamide, and ethambutol (RIPE therapy). The **rifamycins** commonly cause **harmless red-orange discoloration** of body fluids (urine, sweat, saliva, tears), which explains this patient's symptoms. They inhibit DNA-dependent **RNA polymerase**, thereby preventing transcription and leading to a deficiency of proteins necessary for mycobacterial survival. Structural alteration of this DNA-dependent RNA polymerase induces bacterial **resistance**. Unlike isoniazid, rifamycins are not specific to mycobacteria.

(Choice A) Structural alteration of enzymes involved in DNA winding-unwinding would promote resistance to fluoroquinolones, drugs that bind and inhibit DNA gyrase in bacterial cells, causing fracture of the DNA chain.

(Choice C) Antibiotics that act on the ribosome can be divided into those that act on the 50S subunit (eg, chloramphenicol, clindamycin, linezolid, macrolides) and those that act on the smaller 30S subunit (tetracycline, doxycycline, aminoglycosides).

(Choice D) Decreased bacterial catalase-peroxidase activity is a mycobacterial response to isoniazid. Before it can inhibit mycolic acid synthesis, isoniazid must be converted to its active form by the mycobacterial catalase-peroxidase enzyme.

(Choice E) Upregulation of beta-lactamase synthesis would cause bacterial resistance to beta-lactam drugs such as penicillins, aminopenicillins,

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(Choice E) Upregulation of beta-lactamase synthesis would cause bacterial resistance to beta-lactam drugs such as penicillins, aminopenicillins, cephalosporins, and monobactams. Infections caused by organisms expressing beta-lactamase require the addition of a beta-lactamase inhibitor (eg, clavulanic acid, sulbactam, tazobactam) or the use of a carbapenem.

Educational objective:
The rifamycins block the action of the bacterial DNA-dependent RNA polymerase, thereby inhibiting transcription. Resistance is acquired by modification of the rifampin binding site on the bacterial DNA-dependent RNA polymerase. Common side effects include hepatotoxicity, blood dyscrasias, and harmless red-orange discoloration of body fluids.

Pharmacology	Infectious Diseases	Tuberculosis
Subject	System	Topic

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